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REACTING CELLS IN THE BRAIN IN THE PRESENCE OF A FOREIGN BODY

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In attempts (by Dr. Oldberg) to obstruct the sylvian aqueduct according to the method of Dandy [1] (by way of the fourth ventricle), the pledgets of cotton used for this purpose were occasionally pushed sideways into the nerve parenchyma (fig. 1). Figure 1 shows such a pledget below a transverse slit (above, at *IV*) representing a continuation of the fourth ventricle, which was also found to be obstructed by pledgets of cotton (in five specimens). Where the pledget of cotton obstructed the fourth ventricle, a part of the caudal part of the sylvian aqueduct was invaded. In both locations the presence of the foreign body gave rise to the formation of several varieties of reacting cells. The reacting cells were fundamentally different from those that arise around plugs of necrosed, coagulated tissue produced by plunging into the brain a hot needle, a sharp knife, a spicule of bone or a similar irritant. The brains of eight dogs have been studied histologically. The animals, which apparently felt no discomfort from the presence of an intracerebral foreign body, died or were killed from one, five or twelve days to six months after the operation.

MICROSCOPIC OBSERVATIONS

Even under a low power lens, one could see a dense ring (fig. 1) more or less enveloping the area occupied by the cotton and bordered in some places by a lighter, limiting zone (*L.Z.*), which merged with apparently intact brain tissue. In some parts of the plugs, the peripheral ring and the adjacent limiting zone, under a higher power lens (fig. 2), one could detect foci of inflammatory cells (at *L*), minute hemorrhages and some changes in the cerebral parenchyma itself. In each of the aforementioned areas (the plug, the enveloping ring, the hemorrhagic

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1. Dandy, W. E.: Experimental Hydrocephalus, Tr. Am. Surg. A. **37**:397, 1919.

areas and the limiting zone), reacting cells were in evidence. They varied in each area, as though reflecting the type of tissue involved.

Reacting Cells in the Area Occupied by the Pledget of Cotton.—The pledget shown in figure 1 (in place for twenty-one days) exhibited, under a high power lens, numerous scattered cotton fibers in the form of bands (fig. 2) of varying

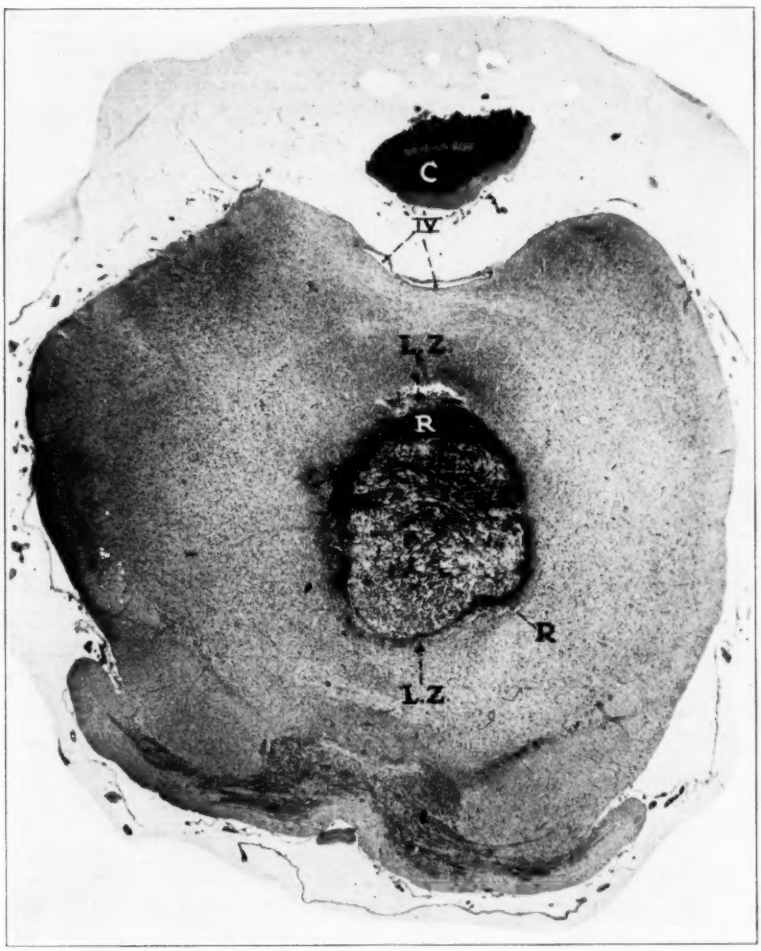

Fig. 1.—A pledget of cotton is shown in the center, underneath the fourth ventricle (*IV*). *R R* indicates the dense dark ring; *L.Z.*, the limiting zone and *C*, a fragment of the cerebellum. Toluidine blue stain.

size and thickness. Practically each fiber or a portion of a fiber was covered by fibroblasts, the nuclei of which were round or oval and rich in chromatin. The nuclei were gathered in clusters around some fibers, while other fibers, especially larger ones, appeared to be plastered by the nuclei (fig. 3). The fibroblasts were intermingled with large cytoplasmic cells, some of which were multinucleated (figs. 3 and 4). They were striking not only for their huge size and the large number of nuclei but also for enclosures within their cytoplasm.

The inclusions were small fragments of cotton fibers, which either lay within vacuoles of the cell bodies or were engulfed by the processes of the cell bodies (fig. 4), much resembling the reactions described by Metchnikoff [2] in protozoa and primitive ameba-like organisms invaded by small foreign bodies. In other cells, in which the larger part of the cytoplasm was taken up by a fragment of a cotton fiber, the nuclei were arranged at the periphery in the form of a

Fig. 2.—*L* indicates a focus of inflammatory cells (lymphocytes and plasma cells); the bands are cotton fibers scattered among the nuclei of fibroblasts. The colorless spaces rather poor in nuclei are scars of connective tissue. Toluidine blue stain.

horseshoe (fig. 5). Especially numerous were the huge cells at the marginal areas of the pledget, which were always mixed with cotton fibers. Such large multinucleated cells were analogous to giant cells around foreign bodies else-

2. Metchnikoff, Élie: Léçons sur la pathologie comparée de l'inflammation, Paris, G. Masson, 1892.

where in the body and are known as foreign body giant cells (Langhans cells). In the center of the foreign body, where fragments of cotton fibers were scarce, giant cells were also scarce; they were absent near cotton fibers that were not fragmented and were well preserved (fig. 2). In such areas there were in evidence either fibroblasts mixed with mast cells or strands of connective tissue fibers which transformed the center of the cotton pledget into a solid

Fig. 3.—Large fibers in the upper left corner of the figure are plastered by fibroblasts; in the center of the lower half of the picture is a multinucleated giant cell; at *F* curled cotton fibers are surrounded by fibroblasts. The colorless area around the giant cell is a connective tissue scar covered by nuclei of fibroblasts. Toluidine blue stain. The inclusions can be seen better in figures 4 and 5.

connective tissue scar (figs. 5 and 6). With the staining method of Van Gieson, it was possible to demonstrate the absence of any connection between the connective tissue fibers and the giant cells. They are independent structures.

A small section of the area of the pledget (figs. 2 *L* and 6 *P*) exhibited dense foci of hematogenous elements—lymphocytes and plasma cells—many of which were vacuolated (degenerated). In general, they were typical, and for this reason they require no special description. Plasma cells were also encountered along minute fragments of cotton fibers, among macrophages and were mixed with

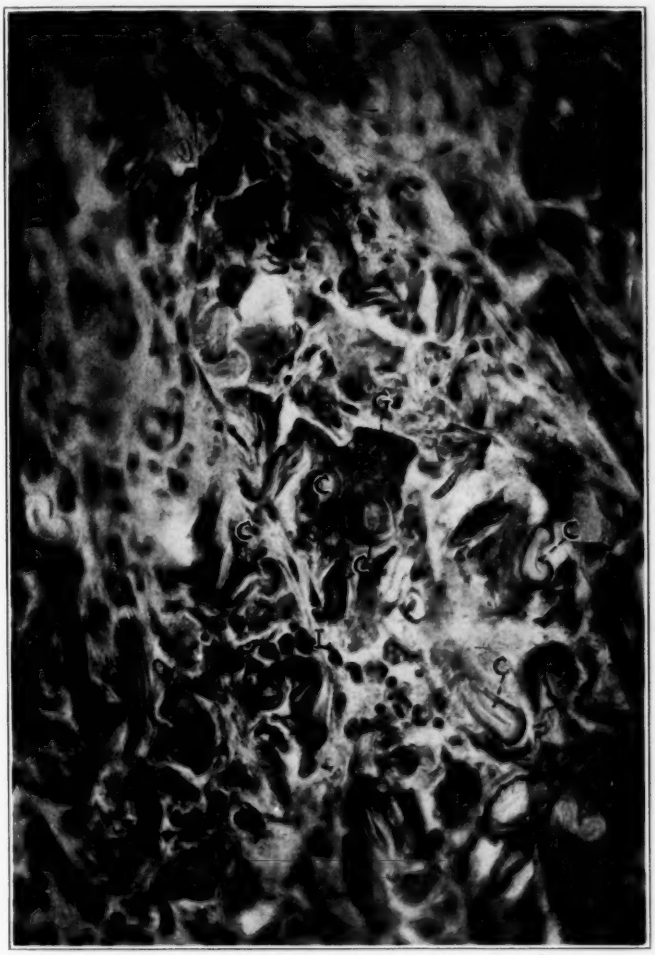

Fig. 4.—The curled or folded formations are fibers of cotton (*C*) enclosed within giant cells (*G*), as if engulfed by their processes. *L* indicates lymphocytes and plasma cells. In the lower left half can be seen a small part of the pledget, with many cotton fibers, partly free and partly as inclosures. Toluidine blue stain.

fibroblasts, mast cells, giant cells and even gitter cells. However, the purely inflammatory hematogenous elements—lymphocytes and plasma cells—were by far the most numerous in the foci marked *L* (fig. 2) and *P* (fig. 6). In specimens from animals that died early, within from one to eight days after the operation,

the main reacting cells were lymphocytes, plasma cells, macrophages and fibroblasts. No giant cells or gitter cells were in evidence.

Blood vessels were generally scarce, especially in the area transformed into a connective tissue scar. The vessels were hyperemic; their endothelial and adventitial cells stained brightly and appeared to be hypertrophied, and the adventitial spaces were devoid of infiltrations of cells, fragments of cotton or giant cells.

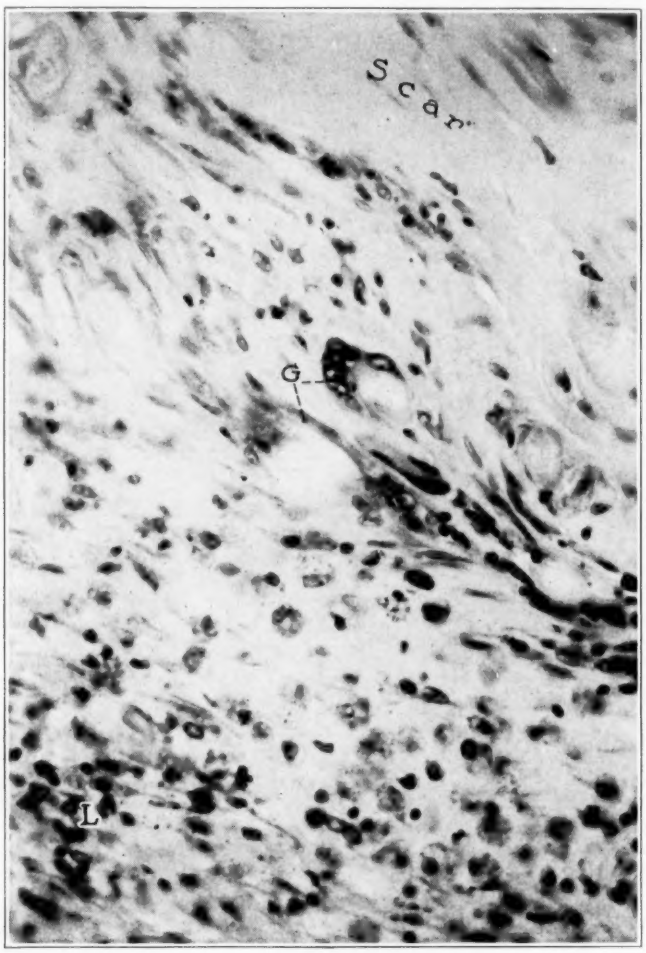

Fig. 5.—In the upper third of the figure two giant cells (*G*) containing fragments of cotton fibers and their nuclei are arranged in the form of a horseshoe. In the upper part of the figure there are a solid connective tissue scar and some fibroblasts. In the lower half, below the giant cells, is a portion of the ring (fig. 1), with numerous gitter cells, lymphocytes (*L*), some macrophages and fibroblasts. Toluidine blue stain.

The nerve parenchyma which harbored the cotton was practically destroyed. Few ganglion cells, especially those situated at the periphery of the pledget, were preserved, and those that remained were profoundly changed. Some were swollen

and pale; others were vacuolated or liquefied and hardly recognizable. Their dendrites, which were also vacuolated, were short, swollen and generally very scarce. The Nissl bodies were broken up; some cells were entirely devoid of them, and others exhibited such marked phenomena of neuronophagia that sometimes it was not possible to tell at first glance whether one dealt with a multi-

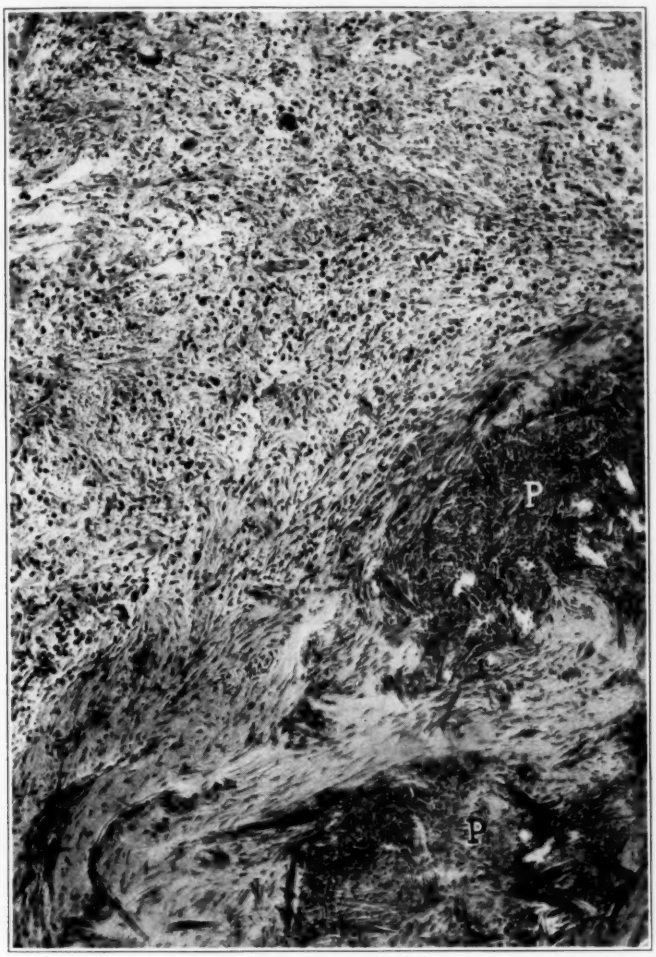

Fig. 6.—The numerous dark round bodies in the upper portion of the figure are macrophages (shown in higher magnification in figure 8). Bands of connective scar tissue separate the area of macrophages from fragments of the plug, at *P*, showing cotton fibers and numerous lymphocytes.

nucleated giant cell or a ganglion cell in a state of neuronophagia. Occasionally a gitter cell was encountered among preserved ganglion cells.

The foregoing changes in nerve tissue caused by the presence of a pledget of cotton may be summed up as phagocytosis of broken-up cotton fibers by giant

cells and their isolation and encapsulation by fibroblasts and connective tissue fibers. Though the most striking reacting cells were represented in the plug by foreign body giant cells, the reacting cells in some parts of the plug were purely inflammatory—lymphocytes and plasma cells.

Reacting Cells in the Peripheral (Enveloping) Ring.—The ring, or the periphery, of the pledget (figs. 1 and 5) consisted mainly of lymphocytes, fibroblasts, macrophages and, especially, gitter cells. The latter were also numerous outside the ring, in a rarefied area, the limiting zone (fig. 1, *L.Z.*), extending into the apparently normal brain tissue, separating the latter from the plug and its enveloping ring. The gitter cells here were of the classic gamma variety described by Jakob.[3] The cells were round; their nuclei were eccentric and rich in chromatin granules, and the cytoplasm was devoid of processes and was honeycombed (fig. 7). The cytoplasm consisted of minute vacuoles, regular and of the same form and size (in the majority of the cells), and all were packed with lipoids. Such gitter cells are mobile elements, their mobility being, so to speak, passive, as they are slowly carried from place to place by the tissue currents of the cerebral parenchyma. This type of gitter cell denotes an advanced stage of nerve degeneration and was absent in specimens from dogs that died in from one to twelve days after the operation. Instead, there were other gliogenous formations: myelophages (large vacuolated bodies) and gitter cells (types alpha and beta) representing the so-called prestages of the classic gitter cells. In specimens from dogs that died from three and one-half to six months after the operation the prestages of gitter cells were not in evidence, for all had become converted into the classic type previously described.

Preeminent as the gitter cells were, giant cells and fibroblasts were also noted among them, but only occasionally. The latter were present as bipolar elements, often arranged in parallel bands enclosing rows of gitter cells (fig. 7).

Reacting Cells in a Zone Between the Ring and the Intact Brain Tissue (figs. 1 and 2).—Such a zone was observed by Farrar [4] in the cerebral cortex of rabbits in which he introduced minute platelets of elder marrow, 40 microns thick, through an incision in the dura, pia and cortex. He aptly called it the limiting zone. In this zone small foci of hemorrhage were present among numerous hyperemic blood vessels. In this area, aside from red cells, there were many vacuolated round cell bodies (figs. 6 and 8), which harbored within their vacuoles fragments of erythrocytes, granules of broken-down hemoglobin and other badly staining substances, which were ill defined. In general, such formations were what Metchnikoff [2] termed macrophages, also known under many other names (the most popular of which is histiocyte). Under certain circumstances these formations assume a large size and form giant cells. The macrophages were intermingled with microglia cells, which were typical even when stained with toluidine blue (fig. 8 *M*).

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3. Jakob, A.: Ueber die feinere Histologie der sekundären Faserdegeneration an der weissen Substanz des Rückenmarks, in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1912, vol. 5, p. 1.

4. Farrar, C. B.: On the Phenomena of Repair in the Cerebral Cortex: A Study of Mesodermal and Ectodermal Activities Following the Introduction of a Foreign Body, in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1908, vol. 2, p. 1.

Typical and numerous as the microglia cells were, they exhibited no transitional forms to gitter cells, nor did they exhibit inclusions, such as red cells or other broken-down tissue. This function was exercised solely by the macrophages. The origin of the latter, whether it was hematogenous or histogenous, could not be determined in my specimens.

Fig. 7.—The gitter cells shown are mostly of the gamma type. *G* indicates a gitter cell with larger vacuoles, a transition to the classic gitter cell type. The oblong dark nuclei and processes are fibroblasts. The cells should be contrasted with those shown in figure 8. Van Gieson's stain.

Changes in the Cerebral Parenchyma.—No noteworthy changes were detected in the cerebral parenchyma outside the plug and the limiting zone. The ganglion and glia cells and the blood vessels were normal. The only interesting feature was a wealth of rodlike and sausage-like microglia cells scattered throughout the

parenchyma, especially in the vicinity of the limiting zone. The microglia cells were mostly interfascicular, situated along the nerve fibers, and were also distributed along the adventitia of the blood vessels and the capillaries. Some were typical microglia cells, even when they were stained with toluidine blue, but, as in other areas, they exhibited no phagocytic activities.

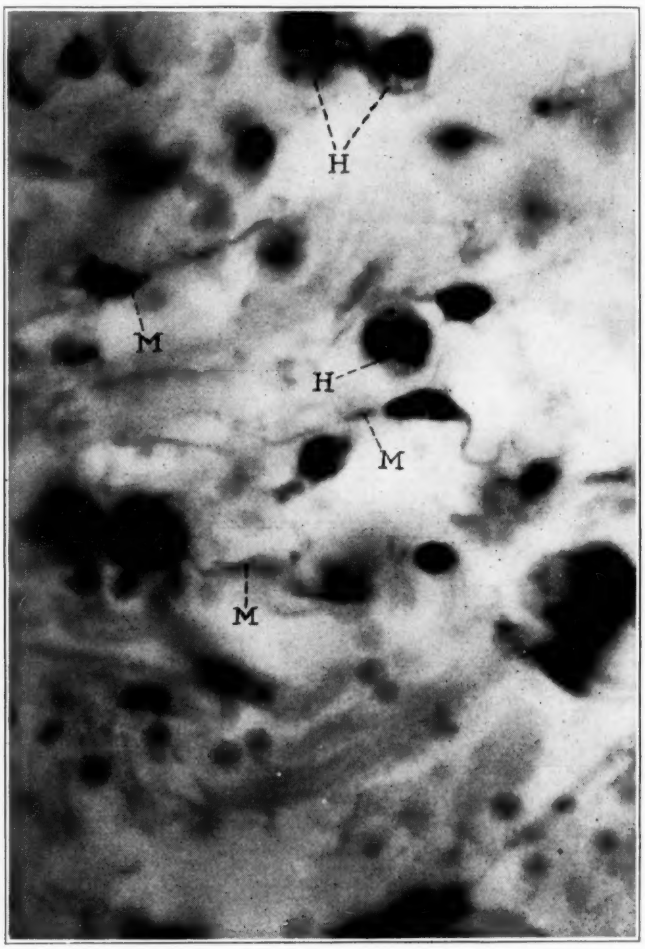

Fig. 8.—The large round cells (*H*) with inclusions are histiocytes (macrophages); some are out of focus. This figure is a higher power magnification of the dark bodies in figure 6. Some typical microgliocytes (many out of focus) are indicated at *M*, but no transitional forms to gitter cells were present. Toluidine blue stain.

Reacting Cells Caused by a Cotton Pledget in the Fourth Ventricle.—The reacting cells and histologic changes that were produced by the plugging of the fourth ventricle were analogous to those already described: foreign body giant cells, fibroblasts, mast cells, gitter cells and macrophages. The choroid plexus

of the fourth ventricle was compressed, but its stroma exhibited no reactive changes. The tuft cells appeared to be reticular, and the ependymal cells were several layers thick. The pledget was in contact with only a small part of the parenchyma, where the changes took place as already described. The type of reacting cells differed, depending on the time element. In specimens from dogs that died five or seven days after the operation, giant cells and gitter cells were not in evidence, but plasma cells, fibroblasts and macrophages were numerous. The macrophages were usually packed with granules of blood pigment, and those that were devoid of contents resembled gitter cells on superficial examination. Typical gitter cells, however, were not present. In specimens from a dog that died after twelve days, macrophages and foreign body giant cells were numerous. Fibroblasts were more numerous, while lymphocytes and plasma cells were rare, and gitter cells were absent. In short, lymphocytes and plasma cells were prominent in the early days after the operation, giant cells appeared about the eighth day, and typical gitter cells showed still later, not before two weeks, while fibroblasts were abundantly represented in all phases, whether recent or late.

The subarachnoid space, especially after obstruction of the fourth ventricle, was more or less dilated and was always infiltrated with lymphocytes, polyblasts and gitter cells.

COMMENT

The changes produced in the cerebral parenchyma by the insertion of a pledget of cotton permit studying the types of reacting cells more conveniently than is possible in an experiment requiring a more complicated and severer injury (opening of the cranium and infliction of a massive injury by plunging into the brain a hot or cold needle, a knife, etc.). Additional irritations, with an excessive influx of mesodermal elements, is thus avoided. On the whole, the changes, regardless of their duration, may be considered inflammatory, as evidenced by the presence of immense numbers of lymphocytes and plasma cells, especially in the early stages of the experiments. Especially marked were the inflammatory changes in the area directly attacked by the inserted foreign body, while in the vicinity of the foreign body the changes were partly degenerative and partly resembled minute hemorrhages. Though the types of reacting cells varied somewhat, depending on the tissues affected and the duration of the injury, their significance was the same —to rid the brain of the foreign body, the broken-up nerve tissues and the hemorrhages. It is evident that each of the three forms of pathologic tissue mentioned was attacked by a different type of phagocyte: the cotton pledget, by the foreign body giant cells, fibroblasts and solid connective tissue; the degenerated nerve tissue, by gliogenous gitter cells, and the blood, by macrophages (histiocytes). One is tempted to assume that all the reacting cells mentioned (foreign body giant cells, fibroblasts, gitter cells and macrophages) are analogous structures, the difference in their size and shape being due to the several types of pathologic tissues attacked. While this is true of their function, it is not altogether true of their histogenesis, for the foreign body giant cells,

fibroblasts and macrophages, all mesodermal elements, may under certain conditions differ from gitter cells histogenetically. For instance, in the conditions under discussion, the gitter cells were not mesodermal (microglial) but glial elements. Though it is generally conceded that gitter cells may be mesodermal and arise from macrophages or histiocytes, they are, according to some investigators, especially Hortega [5] and his numerous followers, the products of the microglia cells only (Hortega cells). According to Hortega, microglia cells are the histiocytes of the central nervous system, in which they represent the reticulo-endothelial system. He maintained that under no circumstances do the glials, whether cytoplasmic or fibrillary or as oligodendroglia, participate in the clearing away of the products of degeneration, be they blood cells, blood pigment, lipoids or broken-down nerve tissue, for such abnormal products, according to him, are taken care of by the microgliocytes. The function of the microglia cells is thus the same as that of the foreign body giant cells and histiocytes elsewhere in the body. While such a theory would place in one group all the types of phagocytic phenomena, whether they occur in the central nervous system or outside it, there are facts which suggest exceptions to the teaching that all gitter cells are microglial, that "microglia provide the various forms of mobile phagocytes present in every area of cerebral destruction and in many pathological processes." [5b] In the present experiments, for instance, microglia cells were inconspicuous as reacting cells, regardless of the type of tissue involved (blood, the foreign body or the nerve tissue); they did not exhibit the slightest signs of reaction, such as changes in their processes or in the size and shape of their nuclei or cell bodies. Because of the absence of such transitional forms and because of the fact that the microglia cells that were occasionally seen were normal, one is hardly justified in assuming that the gitter cells scattered among them were modified microgliocytes.

Gitter cells may develop from glia (oligodendroglia) cells and may resemble similar cells formed by microglia cells, but the resemblance exists only in the terminal, fully developed stages. As a rule, however, both types of gitter cells exhibit evolutional morphologic differences. As indicated in figure 9, microglial gitter cells are polymorphic. They may be angular, curved or irregular; their nuclei are not always, in fact are seldom, eccentric, and their vacuoles are usually not uniform, as in the classic gitter cells shown in figure 7. The contents of the microglial gitter cells may be composed of various substances—blood, granules

5. (*a*) del Rio Hortega, P.: Concepts histogénique, morphologique, physiologique et physio-pathologique de la microglie, Rev. neurol. **1**:956, 1930. (*b*) del Rio Hortega, P., and Penfield, W.: Cerebral Cicatrix: Reaction of Neuroglia to Brain Wounds, Bull. Johns Hopkins Hosp. **41**:278, 1927.

of hemosiderin, broken-down lymphocytes or lipoids—but never of nerve tissue. Thus, Marchi globules, myelophages or transitional gitter cells, as seen in secondary nerve degeneration in man or in experimental animals, have never been described within, or in connection with, microglial gitter cells. Giant or syncytial myelophages, so well described by Jakob as observed in tissue from experimental animals and also in human tissue,[6] have never been traced to microgliocytes. But it is possible to trace

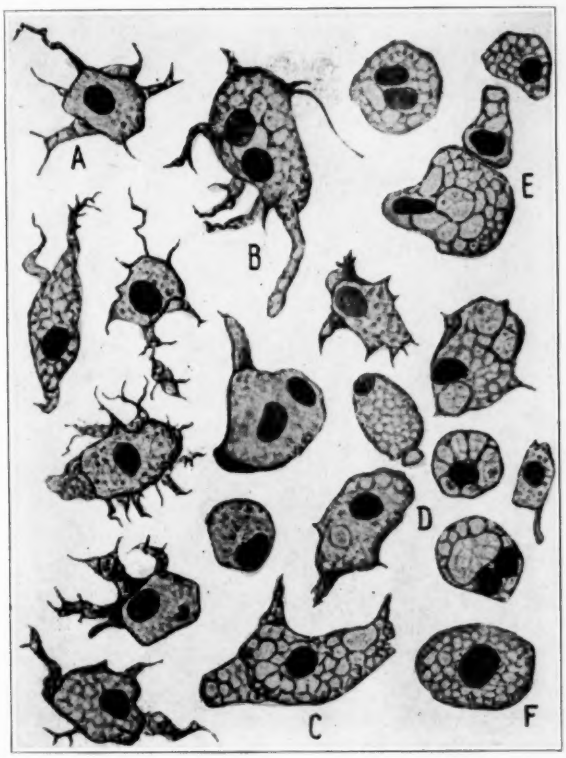

Fig. 9.—Gitter cells formed by microglia cells are shown in the ultimate phases. *A* is a microglia cell, with preservation of some prolongations; *B* is a cell with two nuclei, and *C*, *D*, *E* and *F* are globoid forms, showing their peculiar structure. (According to Hortega: *Trab. d. lab. de invest. biol. Univ. de Madrid* **18**:69, 1920.)

the foregoing changes, culminating in the formation of gitter cells, to the glia and to show that only the glia displays phagocytic activity in

6. Hassin, George B.: Histologic Changes in Amyotrophic Lateral Sclerosis, M. Rec. **91**:228 (Feb. 10) 1917; Studies in the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **7**:589 (May) 1922; Histopathology of the Peripheral and Central Nervous Systems, Baltimore, William Wood & Company, 1933.

conditions in which nerve degeneration is a prominent phenomenon (amyotrophic lateral sclerosis, multiple sclerosis, subacute combined degeneration of the cord and many other pathologic states). In figure 10, for example, a myelophage (*M*) is shown. It is formed by an oligodendrocyte, the fibers of which, emanating from the region of the nucleus (*N*), form a ring (*P*) enclosing two fragments of an axon. The myelophage is destined to become a gitter cell harboring the same nerve fragments but in the form of lipoids; it is an early stage of a gitter cell. When the degenerated nerve tissue is transformed into lipoids, it is replaced by a scar which consists only of glial tissue, while the scar caused by severe injury to the central nerve tissue (stab wound, hemor-

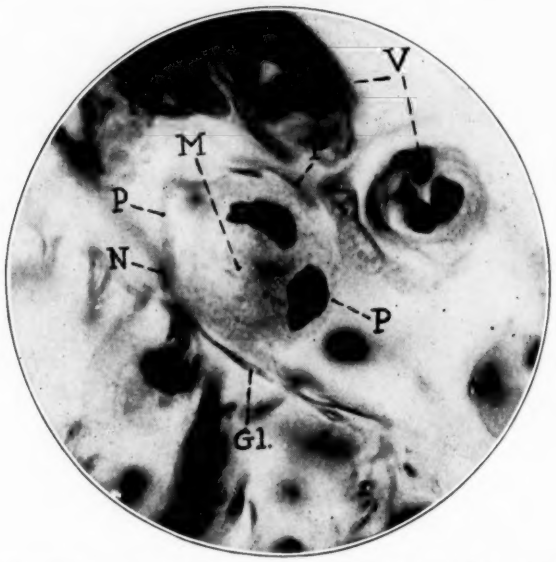

Fig. 10.—In the middle of the figure is a myelophage (*M*), which is a large vacuolated body, the processes (*P*) of which emanate from the nucleus (*N*), an oligodendrocyte forming a ring around the enclosures of myelin (two dark fragments). This section (Hassin, George B.: Histopathologic Findings in a Case of Superior and Inferior Poliencephalitis, Arch. Neurol. & Psychiat. **5**:552 [May] 1921) is from the brain of a patient with so-called superior and inferior polioencephalitis. Bielschowsky's stain; × 1,200.

rhage, softening or laceration) consists of connective tissue and some cytoplasmic glia. In short, reacting cells seen following central nerve degeneration are glial; those seen following severe injury to the central nerve tissue are microglial. While, as has been mentioned, the microglial reacting cells exhibit all kinds of inclusions, except nerve tissue, the glial reacting cells never harbor such inclusions as blood cells or hemosiderin, but only nerve tissue, either undigested or transformed into lipoids.

Lipoids may also be present in microglial gitter cells but are not produced by these cells from broken-up nerve tissue. They are merely picked up by them already formed. This is especially well seen in so-called softening of the brain, or of the spinal cord, that results from ischemia, trauma, large hemorrhages, severe infection or intoxication. For instance, in cases of vascular occlusion gitter cells appear early (twenty-four hours) and in immense masses. They cannot originate locally, that is, at the place of the lesion, for in the latter not only the nerve elements but also the glia cells, the mesodermal structures, including the microglia cells, and the blood vessels become involved and are rendered as helpless as the parenchyma itself. Reacting cells, microglia cells and fibroblasts, stream in large numbers to the site of the lesion from the immediate neighborhood or from remote regions and pick up the damaged nerve tissues that were already converted into lipoids (as the result of the deficient blood supply). To accomplish this, glia cells would require weeks, while microglia cells do not produce lipoids from nerve tissue at all. Lhermitte and Schaeffer [7] and Roussy, Lhermitte and Oberling [8] also emphasized that the mesodermal cells are the first to react in cases of vascular cerebral softening. Such mesodermal cells are microglia cells, which these authors considered glial structures. This is not correct, for, aside from the reasons so ably advanced by Hortega and his followers, there are some other facts which speak in favor of the mesodermal origin of microglia. Thus, I have seen typical microglia cells in the peripheral nerves; Asua [9] noted them in a normal human spleen and in lymph glands, especially in cases of lymphosarcoma; Gozzano [10] observed them in the connective tissue of the choroid plexus, and Visintini [11] noted them in the myocardium of rabbits. While it is unquestionable that gitter cells may be of microglial origin, it is safe to assume that such cells arise only in severe and acute pathologic processes in contrast to the gliogenous type, which develop slowly and only in subacute or chronic degenerative nerve lesions. The absence of gliogenous gitter cells in some of the experiments reported here was due not so much to the character of the injury as to its short duration (from one to five days); the abundance of the cells was marked in tissues in

7. Lhermitte, J., and Schaeffer, H.: Les phénomènes réactionnels du ramollissement cérébral aseptique, leurs caractères différentiels d'avec l'encéphalite compliquée de ramollissement, Semaine méd. **30**:24, 1910.

8. Roussy, G.; Lhermitte, J., and Oberling, C.: La névroglie et ses réactions pathologiques, Rev. neurol. **1**:878, 1930.

9. Asua, F. J.: Die Mikroglia (Hortegasche Zellen) und das reticulo-endotheliale System, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:354, 1927.

10. Gozanno, Mario: Quelques observations de la microglie, Rev. neurol. **1**:1024, 1930.

11. Visintini, Fabio: Sur l'identité morphologique de la microglie avec d'autres éléments histocytaires, Rev. neurol. **1**:986, 1930.

which the injury lasted several weeks or months. When the gitter cells are of mesodermal origin, they are gathered in large and dense foci, which are not broken up by apparently healthy areas, as in tissues showing pure nerve degeneration (multiple sclerosis, amyotrophic lateral sclerosis). Often the areas covered by mesodermal gitter cells represent territories of a definite vascular blood supply, areas never seen with pure nerve degeneration, whether in tissue from human subjects or in tissue from experimental animals.

The difference between the mesodermal and the ectodermal gitter cells may also be seen in the cell types arising in purely local and in remote lesions, as they occur, for instance, in experiments in which two lesions (local and secondary) are produced in the spinal cord. Thus, in rabbits King [12] produced hemisection of the lumbar portion of the spinal cord (local injury), which was followed by secondary degeneration (remote or secondary lesion) of the posterior columns and other tracts. A subcutaneous injection of a solution of trypan blue was given the animals after the hemisection. At the site of the local injury (section of the cord) King found immense masses of "macrophages" (microglia), which became activated by the local trauma. In my experiments no microglial activation took place, for the insertion of a cotton plug is not as powerful an irritant as cutting the cord or brain. The reaction invoked by the inserted cotton sufficed without the microgliocytes. These evidently were not needed and were, as has been demonstrated, replaced in my experiments by giant cells, macrophages and gliogenous gitter cells. When the microgliocytes become activated and invade the place of injury, they immediately pick up débris of broken-up blood or white cells or various dyes, if such have been injected prior, or subsequent, to the making of the lesion (the experiments of Macklin and Macklin [13] and King [12]). Phagocytes packed with vital dyes, which were numerous at the site of the local injury, were not observed by King in the remote areas which had undergone secondary degeneration. This, I think, can be explained by the fact that the phagocytes of these remote areas were not microglial but glial, and glial phagocytes do not take a vital stain. This is in accord with the observations of Rachmanoff [14] that in areas of secondary degeneration the clearing of the tissues is done by the ectodermal (glial) elements, which, as noted, do not take the vital stain.

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12. King, Lester R.: Vital Staining of Microglia, Arch. Path. **19**:656 (May) 1935.

13. Macklin, C. C., and Macklin, M. T.: A Study on Brain Repair in the Rat by the Use of Trypan Blue with Special Reference to the Vital Staining of the Macrophages, Arch. Neurol. & Psychiat. **3**:353 (April) 1920.

14. Rachmanoff, A.: Beiträge zur vitalen Färbung des Zentralnervensystems, Folia neurobiol. **7**:750, 1913.

The foregoing considerations permit of a conclusion that the main reacting cells and phagocytes in the central nervous system are represented by two types of gitter cells. They may sometimes be alike in their terminal stages of development, but they differ histogenetically and physiologically. The ectodermal glial gitter cells, which are the phagocytes for the destroyed nerve parenchyma, are formed by the oligodendroglia cells; the microglia cells (the mesodermal elements) are the phagocytes for the non-nerve tissues (blood, hemosiderin, dyes, fatlike substances, etc.). The function of both types of phagocytes, however, is, as has been emphasized, the same—the removal from the body of substances injurious to health or to life.

CONCLUSIONS

The types of reacting cells in areas of cerebral injury depend on the character of the injury.

In an area of mild injury not associated with a sudden and massive destruction of nerve tissue (as in a case of cerebral or spinal thrombosis), the reactive cells vary according to the type of the irritant (foreign body, for instance). The cells are not microglial, but they may be foreign body giant cells, macrophages, fibroblasts or gliogenous gitter cells.

Microglia cells are not the sole source of gitter cells.

Gitter cells arise from microglia cells in acute, severe neuropathologic conditions (vascular occlusion, trauma, hemorrhage) in which not only the nerve tissue but also the glia succumbs. Gliogenous gitter cells occur only in cases of isolated destruction of nerve fibers, the glia remaining unaffected.

When destruction of the nerve tissue is not massive but selective and limited to single nerve fibers, as in multiple sclerosis or amyotrophic lateral sclerosis, the reaction is also selective and confined to the glia.

Areas of secondary and primary degeneration, such as is seen in some cerebral lesions, amyotrophic lateral sclerosis, multiple sclerosis and subacute combined degeneration of the cord, exhibit the neuroglial type of gitter cell, which also speaks against a vascular factor in their histogenesis, as a vascular factor produces massive destruction of the nerve tissue, with formation of microglial (mesodermal) types of such cells.

CONGENITAL ATRESIA AND STENOSIS OF THE AQUEDUCT OF SYLVIUS

AN ANATOMIC STUDY OF SIX CASES

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The first recorded anatomic observation of a congenitally occluded aqueduct of Sylvius was made by Hilton in 1847.[1] However, Hilton limited his report to a gross description of the occlusion. Since then fairly detailed studies of a considerable number of cases of aqueductal occlusion or stenosis have been reported by Spiller,[2] Guthrie,[3] Schlapp and Gere,[4] Dandy and Blackfan,[5] de Lange,[6] Shelden, Parker and Kernohan,[7] Orton [8] and others.[9] A surprisingly large number of the

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6. de Lange, C.: Klinische und pathologisch-anatomische Mitteilungen über Hydrocephalus chronicus congenitus und acquisitus, Ztschr. f. d. ges. Neurol. u. Psychiat. **120**:433, 1929.

7. Shelden, W. D.; Parker, H. L., and Kernohan, J. W.: Occlusion of the Aqueduct of Sylvius, Arch. Neurol. & Psychiat. **23**:1183 (June) 1930. Kernohan, J. W.: Cortical Anomalies, Ventricular Heterotopias and Occlusion of the Aqueduct of Sylvius, ibid. **23**:460 (March) 1930. Parker, H. L., and Kernohan, J. W.: Stenosis of the Aqueduct of Sylvius, ibid. **29**:538 (March) 1933.

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(Footnotes continued on next page)

patients were adults and older children; only a few were infants in the first months of life. Only a few of the patients showed other developmental anomalies.

The six cases to be described here represent instances of congenital obliteration or narrowing of the iter in very young infants who presented also other developmental abnormalities, such as spina bifida with meningocele or meningomyelocele, clubfoot, webbing and misdirection of the toes and a bifid ureter. Moreover, the material, particularly because of the youth of the patients, made it possible to trace the patho-

TABLE 1.—*Clinical Features*

Case	Age	Sex	Labor and Delivery	Clinical Features	Course
1	2 days	M	Normal	Spina bifida with meningomyelocele (lumbosacral)	Meningomyelocele removed; death on following day
2	3 mos.	M	Breech; protracted labor	Head very large; began to increase in size at 6 weeks of age; total blindness; clonic movements of upper extremities; clubfoot	Death two weeks after admission
3	2 days	F	Normal	Head enlarged; spina bifida with meningocele (sacral); flaccid paralysis of lower extremities	Meningocele ruptured and discharged purulent material; death ten days after admission
4	3 wks.	F	Normal	Head enlarged; spina bifida with meningomyelocele (lumbar); paralysis and anesthesia of lower extremities	Meningomyelocele removed, followed by rapid increase of enlargement of head; death four months after admission
5	2 wks.	F	No history	Spina bifida with meningomyelocele (lumbosacral); flaccid paralysis of lower extremities	Meningomyelocele removed; followed by enlargement of head; turbid cerebrospinal fluid (Streptococcus haemolyticus); death four weeks after admission
6	3 days	M	Internal podalic version	Head enlarged; toes misdirected, the 5th overriding the 4th, the 2d and 3d webbed; opisthotonos; Kernig sign	Death several hours after admission

logic process to intra-uterine life and to a large extent aided in determining the pathogenesis of the lesion.

MATERIAL AND METHODS

The brains of six infants between the ages of 3 days and 5 months were studied (tables 1 and 2). The infants were admitted to the hospital either because of spina bifida or because of hydrocephalus without deformity of the spinal column. In three cases following surgical intervention for meningocele accompanying spina bifida the infant died of some intercurrent infection. In one infant (case 2) an

9. Bourneville and Noir, J.: Hydrocéphalie, Progrès méd. **12**:17, 1900. Dijkstra, O. H.: Nederl. tijdschr. v. geneesk. **74**:5685, 1930. Oppenheim, H.: Ueber eine Bildungsanomalie am Aquaeductus Sylvii, Monatschr. f. Psychiat. u. Neurol. **7**:177, 1900. Touche, M.: Hydrocéphalie interne, Bull. et mém. Soc. méd. d. hôp. de Paris **19**:141, 1902.

extreme internal hydrocephalus resulted in death without surgical intervention. In case 6 syphilitic pneumonia was the direct cause of death.

The brains were fixed in a dilute solution of formaldehyde U.S.P. (1:5). The midbrain was embedded in paraffin and cut serially. The sections were stained with hematoxylin and eosin, and some were stained also by the Van Gieson method. Many blocks were taken from other parts of the brain, embedded in paraffin and stained with hematoxylin and eosin. Some frozen sections were stained by the Globus modification of the silver carbonate method of Hortega and the gold chloride and mercury bichloride method of Cajal.

MICROSCOPIC EXAMINATION

CASE 1.—The aqueduct was patent throughout its entire length, but it was considerably narrowed at the level of the posterior quadrigeminal body. There,

TABLE 2.—*Necropsy Observations*

Case	General	Brain, Gross Observations*	Brain, Microscopic Observations
1	Bronchopneumonia; patent foramen ovale and ductus arteriosus	Many subpial hemorrhages over parietal and occipital lobes	Aqueduct patent but narrowed at one point by proliferation of subependymal glia
2	No observations (autopsy limited to the head)	Cerebral hemispheres represented by two large cystlike structures filled with 600 cc. of clear, colorless fluid	Complete occlusion of aqueduct by proliferation of subependymal glia
3	Fatty liver	Bilateral internal hydrocephalus	Complete occlusion of aqueduct by proliferation of subependymal glia
4	No observations (autopsy limited to the head)	Marked hydrocephalus	Complete occlusion of aqueduct by glial and connective tissue proliferation
5	Acute purulent bronchitis and bronchopneumonia; patent ductus arteriosus; bifid right ureter	Chronic meningitis and ependymitis; internal hydrocephalus	Considerable narrowing of aqueduct by glial proliferation and ependymitis
6	Syphilitic pneumonia; hypertrophy of right side of heart; patent foramen ovale	Marked internal hydrocephalus; generalized ependymitis; organized blood clot from third ventricle to aqueduct; fourth ventricle filled with solidified blood	Considerable narrowing of aqueduct by glial proliferation and ependymitis

* In all these cases the aqueduct on gross section of the brain was noted to be either exceedingly small or closed.

near the roof of the iter, was a tumor-like projection into the lumen, having the character of an ependymal granulation (fig. 1). This protrusion obliterated half the width of the iter. The projection had broken through the ependymal lining, remains of which could still be seen as small cellular islands at the site of perforation. The ependymal lining could be traced over the protruding mass (fig. 2), lining its sides for a short distance. The ependymal cells gradually decreased in height in the more distant parts of the projection. The entire convexity and the peripheral two thirds of the lateral surfaces of the protrusion were devoid of ependymal lining. The projecting mass showed a cellular structure similar to that of the subependymal glia, except for some small undifferentiated cells and a lack of uniformity of arrangement of the cells. Strewn here and there in the protrusion were small groups of cells which appeared to be ependymal cells.

The subependymal zone in the roof of the aqueduct, particularly close to the glial projection, showed an increased number of cells of the types usually found in the subependyma. The subependymal zone of the more ventral parts of the iter, on the other hand, contained fewer cells and was poorly demarcated from the normal central gray matter.

Somewhat more rostrally there was a striking paucity of ependymal cells in the lining of the roof of the aqueduct. From this region a cellular area extended tail-like dorsally, away from the iter, and terminated a short distance away in a large ependymal tube. The ependymal cells lining the remainder of the aqueduct were low cuboidal cells. The subependymal zone of the aqueduct, except for the already described portion overlying the roof, showed no deviation from the normal.

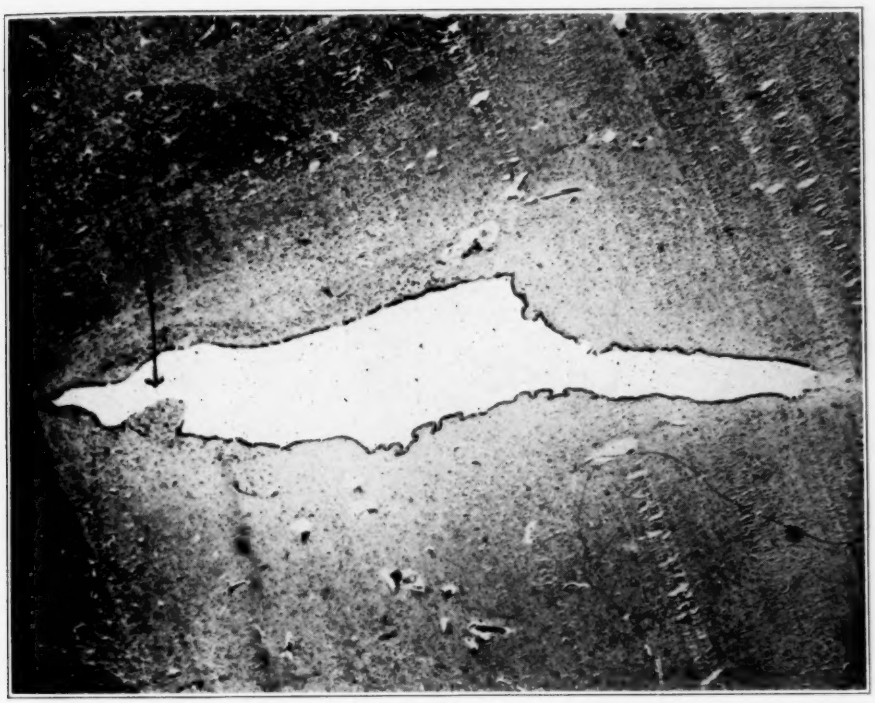

Fig. 1 (case 1).—The aqueduct is narrowed at one point by a glial projection, as shown by the arrow. Hematoxylin-eosin stain; × 24.

There was no evidence of inflammation about the aqueduct or anywhere in the brain.

Comment.—The projection into the aqueduct of Sylvius, as shown in figure 1, was unquestionably a proliferation of subependymal glia. This was demonstrated by the fact that the structure of the protruding mass consisted of glia cells which were similar to those present in the normal subependymal zone, except for some small undifferentiated cells, and by the fact that the projection appeared to continue from the

subependyma without any sign of demarcation. The continuation of ependymal lining along part of the lateral surfaces of the protrusion indicated that the formation of the mass must have been gradual. Finally, the small islands of ependymal cells noted within the projection were evidence of subependymal proliferation.

The absence of inflammatory change either in the subependymal zone or elsewhere in the brain excluded the probability that this intra-uterine proliferation of the subependymal glia was due to an inflammatory process. It is not unlikely that had the child survived the pro-

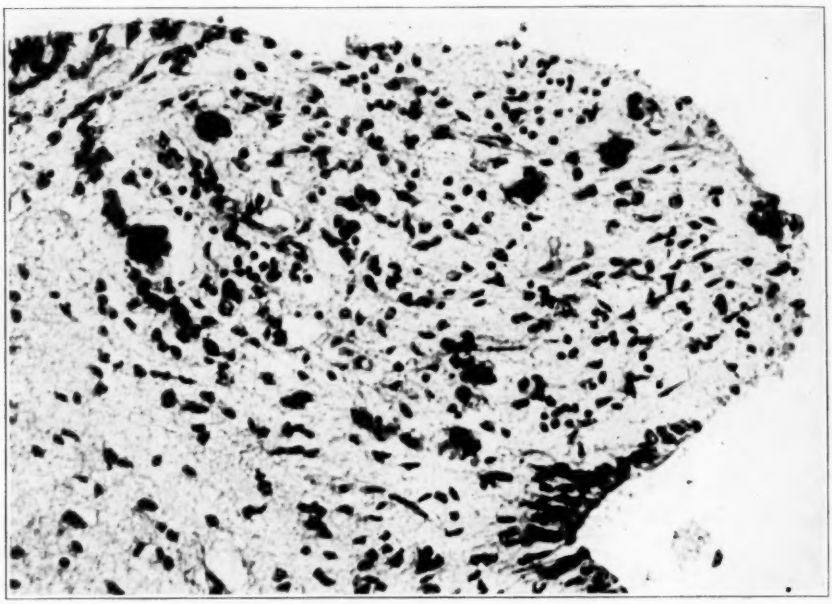

Fig. 2 (case 1).—High magnification of the glial projection shown in figure 1. Hematoxylin-eosin stain; × 280.

trusion would have continued to increase in size and would have formed a bridge across the iter, in a way to be described for cases 2, 3 and 6.

Case 2.—At the level of the anterior quadrigeminal body the ependyma of the aqueduct was highly irregular and flattened in some areas, while in other areas it was either absent or piled up into heaps of two or more layers. At one point, close to the floor of the iter, ependymal cells lining its walls were piled up in masses which projected into the lumen (fig. 3 *A*). Slightly more cephalad a band of glial tissue ran across the aqueduct, dividing it into a ventral, smaller, part and a dorsal, considerably larger, part (fig. 3 *B*). This band of glial tissue showed but few nuclei and no evident increase of glia fibers. The ependymal lining of the smaller subdivision was fairly regular, with the exception of the part covering the band of glial tissue, where it was disrupted. The lining of the larger compartment was highly irregular: strips of well formed ependymal cells alternated

with areas of poorly organized heaps of cells. In some parts the wall of the iter was denuded of ependyma. The large compartment at a more rostral level was in turn divided into smaller lumens by another transverse band of glial tissue (fig. 4 *A*). Similar to the division shown in figure 3 *B*, here also one of the smaller lumens was lined by uniform ependyma, except for a small area adjoining the glial band, where there was a heap of cells. Still further rostrally the smaller compartment had acquired the appearance of an ependymal tubule, while the other compartment, with a distorted lining, was completely blocked by desquamated ependymal and glial cells (fig. 4 *B*). Anterior to that level the iter was markedly dilated.

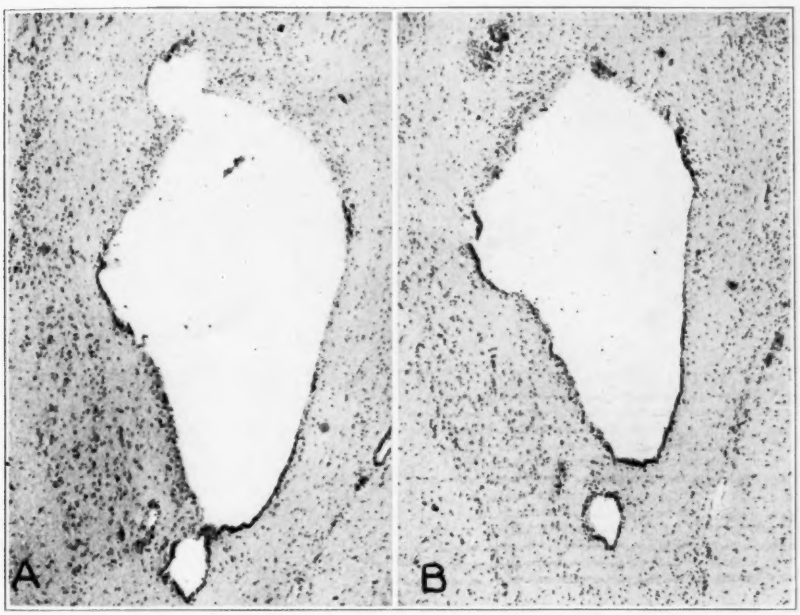

Fig. 3 (case 2).—*A*, a mass of ependymal cells projects into the iter to form a bridge. *B*, a band of glial tissue divides the aqueduct into two compartments. Hematoxylin-eosin stain; × 74.

The subependymal region adjacent to the occluded part of the iter contained a slightly increased number of cells and was surrounded, a short distance away, by a dense band of glia cells, in which there was an occasional ependymal tubule.

There was no evidence of inflammation in the subependymal zone or elsewhere in the brain.

Comment.—This case represents a more advanced stage in the proliferation of subependymal glia described in the previous case. In figures 3 and 4 it is not difficult to follow the subependymal proliferation which had broken through the ependymal lining and displaced the ependymal cells. It is probable that these cells, having an inherent

tendency to form circular structures, in this instance contributed toward the completion of the lumens which had resulted from the proliferation of ependymal cells.

Clubfoot was another developmental anomaly in this case.

Case 3.—At the level of the inferior colliculus the aqueduct was exceedingly narrow (fig. 5 *A*). A large part of the dorsal third of the iter was occluded by a mass of glial tissue containing groups of ependymal cells. The patent part of the iter was lined by ependymal cells which were irregularly shaped and of various sizes. The ventral part of the aqueduct consisted of a large accumulation of distorted ependymal cells.

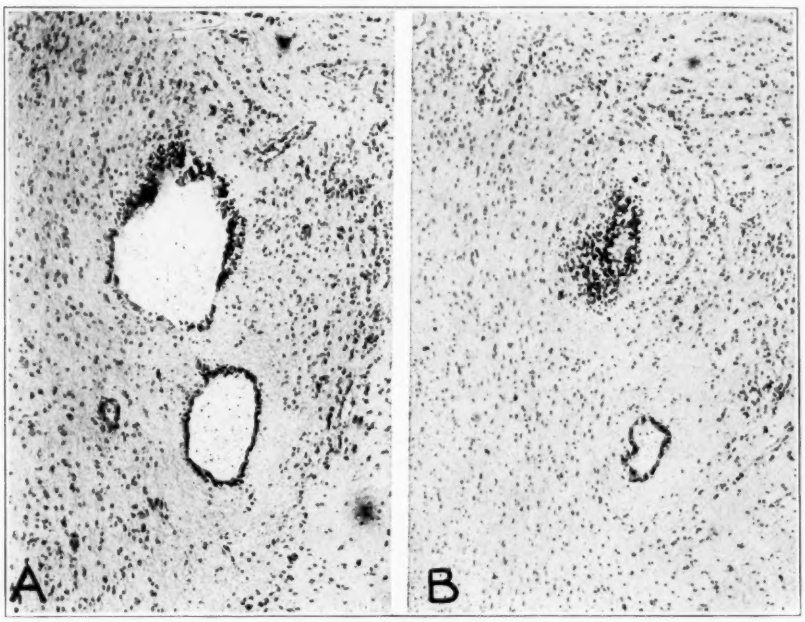

Fig. 4 (case 2).—*A*, the larger compartment shown in figure 3 *B* is here subdivided into two smaller lumens by a band of glial tissue. *B*, the aqueduct rostral to figure 4 *A* consists of an ependymal tubule and a mass of ependymal and glia cells. Hematoxylin-eosin stain; × 74.

At a slightly more rostral level (fig. 5 *B*) the iter was smaller, and at a short distance from the roof small cellular projections extended from the sides of the aqueduct, meeting and fusing in the center, thus forming a band of glial tissue across the iter, separating the roof from the more ventral part.

Still more cephalad (fig. 5 *C*) the only visible traces of an aqueduct were two small ependymal tubules, which were separated from each other by a bridge of glial tissue. These tubules were filled with small deeply stained cells, apparently modified ependymal cells. Anterior to this level the iter was marked by small groups of ependymal cells. The aqueduct, rostral to this complete occlusion, was markedly dilated.

The subependymal zone was of normal structure, and there was no evidence of inflammation there or elsewhere in the brain.

Comment.—In this case also there was evidence that proliferation of the subependymal glia was the cause of the aqueductal obliteration. Figure 5 *A* clearly shows where the subependymal glia had broken through one side of the aqueduct and pushed the ependymal cells of that side over to the opposite side and into heaps in adjacent areas. In figure 5 *B* a protrusion can be followed into the aqueduct, which had broken through the ependymal lining at the site of proliferation.

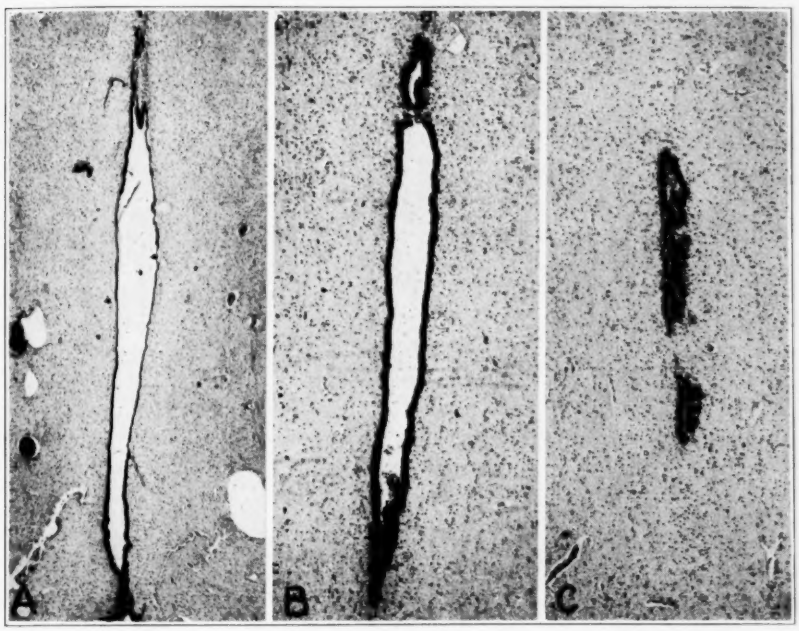

Fig. 5 (case 3).—*A*, the dorsal third of the aqueduct is occluded by glial tissue. Hematoxylin-eosin stain; × 24. *B*, cellular projections extend from the sides and fuse in the center of the aqueduct. *C*, cephalad to *A* and *B* the aqueduct consists of ependymal tubules filled with ependymal cells. Hematoxylin-eosin stain; × 54.

Case 4.—At the level of the anterior quadrigeminal body (fig. 6) the iter was completely occluded by loose glial tissue, which contained a few strands of collagenous fibers. The ependymal lining was absent over several stretches of both sides of the aqueduct, particularly in the dorsal half. At the roof the ependyma had lost its normal appearance, and the cells were piled up in layers two or three cells deep. The lining of the ventral half of the iter had lost its uniformity, the cells assuming various shapes and sizes. The cells were arranged either in single layers or in rows three or four cells deep, occasionally assuming the character of

ependymal tubules. The subependymal zone overlying the areas denuded of ependymal lining contained a few cells and merged with the tissue in the occluded aqueduct.

The iter, rostral to the occlusion, and the third ventricle were considerably dilated. The ependyma was absent over several areas. Where it was present, it was for the most part disrupted and embedded in glial tissue at a distance from the aqueductal channel, particularly in its roof and floor (fig. 7). There the ependymal cells were largely arranged in smaller and larger tubules. The zone immediately subjacent to the roof and the floor of the aqueduct, which were lined by a narrow strip of glial tissue, and to a lesser extent beneath the sides of the iter, was made up of a broad band of areolar tissue (which stained red with Van

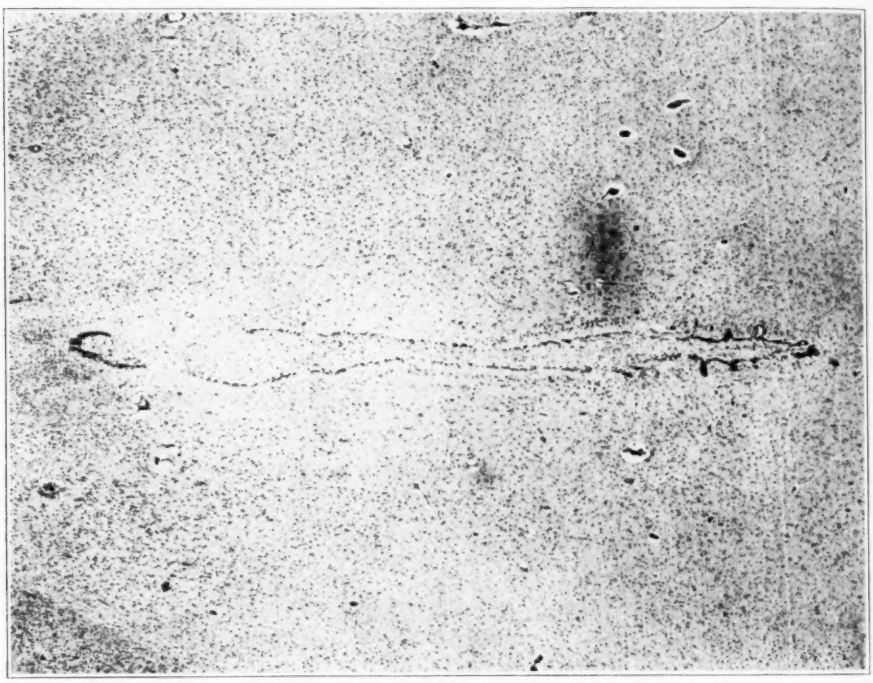

Fig. 6 (case 4).—The iter is completely occluded by loose glial tissue containing strands of collagenous fibers. Hematoxylin-eosin stain; × 26.

Gieson's stain) in which were interspersed subependymal projections and islands of glial tissue.

The dorsal wall of the fourth ventricle (fig. 8) had much the same structure as that illustrated in figure 7, that is, a broad zone of areolar tissue separating the narrow band of glial ventricular lining from the distant ependymal tubules. The ventral wall of the ventricle, on the other hand, showed proliferation of the subependymal glia with little admixture of strands of collagenous fibers.

The lateral ventricles were denuded of ependyma. The lining was made up of thickened glial tissue which over long areas was narrow. Beneath this tissue were islands of areolar tissue resembling the structures illustrated in figures 7 and 8.

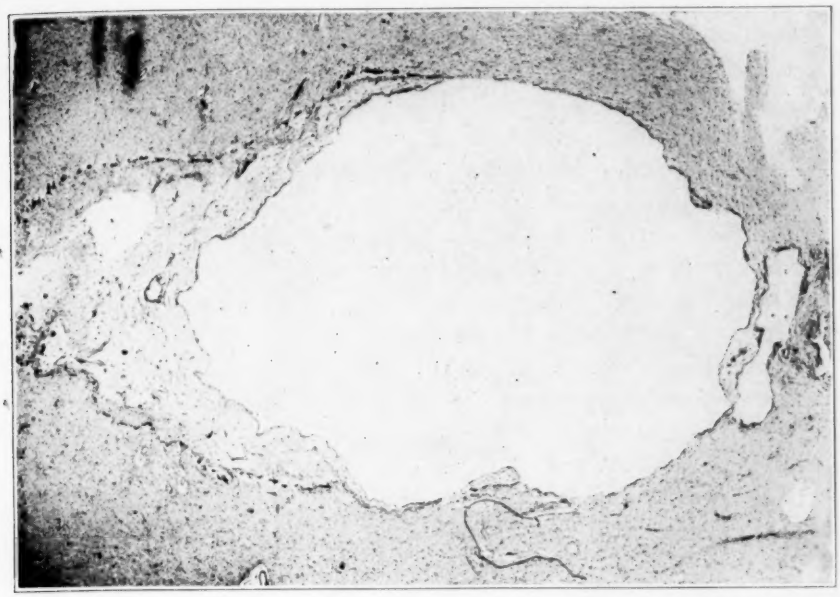

Fig. 7 (case 4).—The aqueduct rostral to the occlusion, showing a zone of areolar tissue in the roof and in the floor. Hematoxylin-eosin stain; × 12.

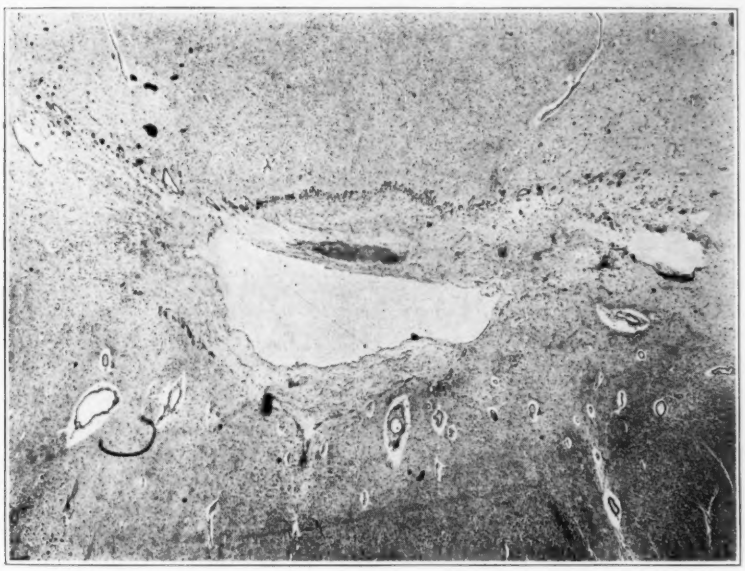

Fig. 8 (case 4).—The fourth ventricle, lined by a proliferation of glial tissue and collagenous fibers. Hematoxylin-eosin stain; × 18.

Comment.—In this case there was complete occlusion of the aqueduct caused by proliferation of the subependymal glia. This was demonstrated by the absence of ependymal lining over certain areas, the piling up of ependymal cells in other areas and the similarity of structure of the occluding tissue and that of the subependymal zone. In addition to this glial proliferation there were areas of areolar tissue which stained red by the Van Gieson method. The structure of this tissue resembled that of the pia-arachnoid and did not have the dense, coarse appearance of reparatory fibrosis. In certain areas the areolar tissue appeared to continue from the pia surrounding vessels in the subependymal zone. It may, therefore, be conjectured that the subependymal projections of glia and islands of glial tissue within the areolar tissue probably proliferated simultaneously with the formation or proliferation of the pia-arachnoid. Therefore, it is highly probable that this developmental error had its origin very early in embryonal life. It is possible that this process continued after birth and led to complete closure of the aqueduct, with subsequent hydrocephalus.

Case 5.—At the level of the inferior colliculus (fig. 9*A*) the ventral half of the aqueduct was patent and of normal size. It showed a normal ependyma and no pathologic changes in the subependymal zone. At the juncture of its ventral and dorsal halves the iter was extremely narrowed and distorted by desquamated glia and inflammatory cells, including phagocytes, which were bound together by bands of fibrin which ran across the iter in all directions from one side to the other. Some such bands could be seen to break through the ependymal lining and either emanate from or penetrate into the subependymal tissue. This area was further narrowed by a large triangular protrusion from the subependyma of one of the lateral horns of the iter. This herniation, which was only partly lined by ependymal cells, consisted chiefly of connective tissue at the apex and part of the base. Immediately adjacent to this structure, in the subependyma, there were zones of what appeared to be astrocytosis. The opposite lateral horn of the aqueduct was absent and was replaced by numerous ependymal tubules surrounded by diffusely arranged glia and ependymal cells. Some vessels showed perivascular mononuclear infiltration. This entire area seemed to have been pushed over toward the iter, thus narrowing its lumen considerably. This area was only partly lined by glia and inflammatory cells, in addition to numerous phagocytes. The subependymal zone of the roof consisted of what appears to be an area of astrocytosis.

At the level of the anterior quadrigeminal body (fig. 9*B*) the ependymitis involved the entire aqueduct, the dorsal third more than the ventral two-thirds, however. The ependyma of the dorsal third of the iter had been pushed away from the lumen by proliferation of the subependymal glia, which had formed a reticular structure immediately lining that area. The ependymal cells formed tubules and clumps of cells. The lining of the ventral two thirds of the iter, however, was normal except for several minute breaks, through which subependymal glia and inflammatory cells entered the lumen. The iter was in great part filled with phagocytes and inflammatory cells, held together by fibrin.

The fourth ventricle was of normal size and appearance and showed only a minute quantity of cell débris, probably carried there from more rostral regions by the cerebrospinal fluid.

The markedly dilated lateral ventricles showed extensive ependymitis, considerably more marked than that of the iter. There was moderate chronic meningitis.

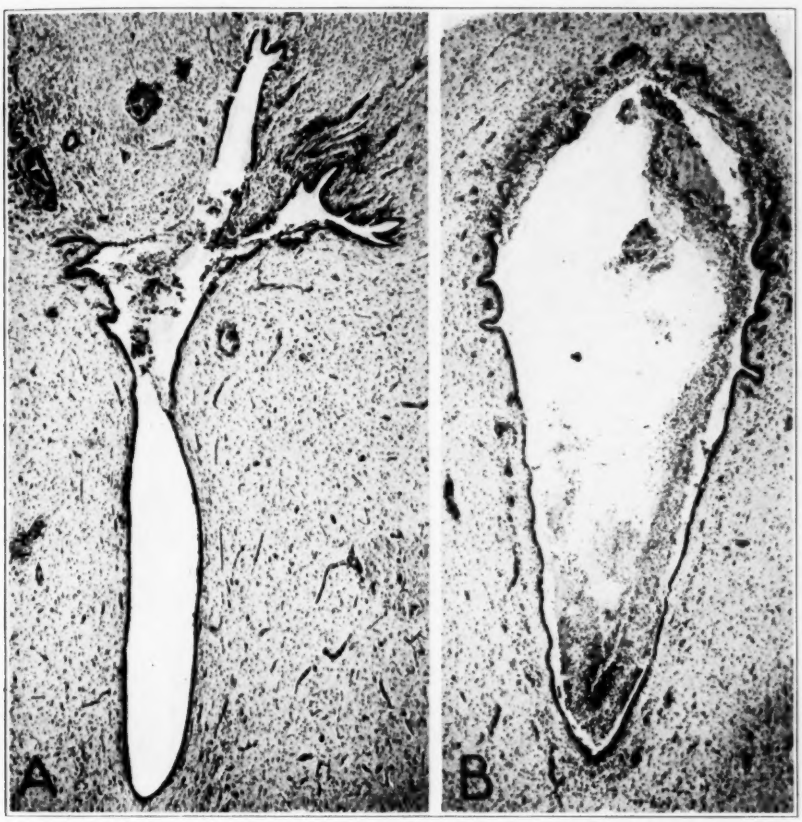

Fig. 9 (case 5).—*A*, the ventral half of the aqueduct is normal; the dorsal half is narrowed by ependymitis and proliferation of the subependymal glia. *B*, rostral to *A* the entire aqueduct is involved in the ependymitis. Hematoxylin-eosin stain; × 46.

Comment.—Because of the coexisting ependymitis the question will be raised as to whether the narrowing of the aqueduct antedated the inflammatory process or was entirely due to it. The ependymitis was most extensive in the lateral ventricles and continued to the aqueduct. At the level of the superior colliculus the entire iter was involved in the inflammatory process, whereas at the level of the inferior colliculus

the ependymitis was limited to the dorsal half, which was the stenosed part. The ventral half of the iter was entirely free from inflammation. If the dorsal half of the aqueduct had not been stenosed, the entire aqueductal ependyma would probably have been involved in the ependymitis, as at the level of the superior colliculus, the ependymitis not having been limited to the stenosed part. This factor indicates that the stenosis, which was caused by the proliferation of subependymal glia, antedated the ependymitis. Of significance also was the existence

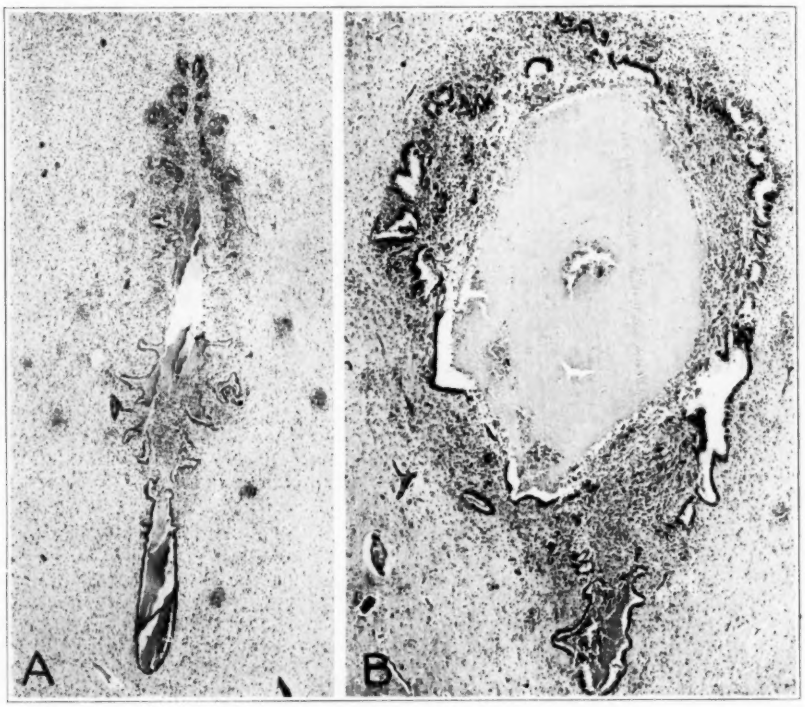

Fig. 10 (case 6).—*A*, the ventral third of the aqueduct is normal; the dorsal two thirds is entirely occluded by ependymitis and proliferation of the subependymal glia. Hematoxylin-eosin stain; × 33. *B*, cephalad to *A* the entire aqueduct is involved in the ependymitis and glial proliferation. Hematoxylin-eosin stain; × 54.

of other developmental defects: spina bifida with meningomyelocele and a bifid ureter.

Case 6.—At the level of the posterior quadrigeminal body (fig. 10 *A*) the aqueduct in its dorsal two thirds was entirely occluded. Glial tissue occupied the entire roof and an area between the dorsal two thirds and the ventral third of the iter. The space between the two occluded areas was occupied by fibrin, which was not clearly demarcated from the glial tissue to which it was adherent, thus indicating that the glial proliferation and the deposit of fibrin took place simultaneously. The cells of the tissue occluding the roof of the iter showed a parallel

arrangement with the long axes parallel to the lateral walls. The cells probably entered the aqueduct by proliferating through the roof and disrupting the lateral wall to form ependymal tubules and clumps of ependymal cells. The other area of glial tissue showed proliferation of cells which had broken through the ependyma of both sides of the iter to form a bridge across the lumen. The neighboring lining was disrupted and had formed ependymal tubules. In addition to glia cells the occluding tissue contained mononuclear inflammatory cells. The ventral third of the aqueduct was patent and had a normal ependyma. The subependymal zone showed numerous small focal and perivascular areas of round cell infiltration, which were seen throughout the entire midbrain.

Slightly caudad the ventral third of the aqueduct was patent and normal. The dorsal two-thirds, however, was markedly dilated and was completely filled with blood in the process of organization and with necrotic and disintegrated tissue, which was previously the brain tissue surrounding the roof of the iter. There were several necrotic areas in the pons.

At the level of the superior colliculus (fig. 10 *B*) the entire aqueduct was surrounded by the proliferation of subependymal glia. The iter was oval, as though the glial proliferation had been halted by the mass of fibrin which entirely filled the lumen. In several areas glia cells were seen in the periphery of the mass of fibrin, and fibrin was noticeable within the glial proliferation, particularly around the floor of the iter, where the larger ependymal tubules were filled with fibrin. The entire ependymal lining had been pushed away from the iter and was in the form of ependymal tubules of various sizes.

Comment.—This case resembles case 5 as in both there was marked ependymitis in addition to a stenosis of the aqueduct. Since the ependymitis was apparently of longer existence than the postnatal life of the child, it is probable that the inflammatory process was of intrauterine origin. As in case 5, the ventral third of the aqueduct at the level of the inferior colliculus was normal and free from ependymitis. The dorsal two thirds, on the other hand, which was the stenosed part, was involved in the inflammatory process. Here, as in the previous case, it must be assumed that the stenosis which was caused by proliferation of subependymal glia preceded the ependymitis. It is probable, however, that the glial proliferation became aggravated by the ependymitis and the intra-aqueductal hemorrhage.

GENERAL COMMENT AND CONCLUSIONS

The pathogenesis of congenital occlusion or stenosis of the aqueduct of Sylvius has been a subject of discussion for many years. In the cases of occlusion or narrowing of the iter by glial tissue two main explanations have been advanced.

1. *An Intra-Uterine Infection Causing a Secondary Proliferation of Subependymal Glia.*—D'Astros [10] stated as his opinion that intrauterine infections particularly affect tissues and organs that are in the early stages of development, resulting in anomalies of various forms.

10. d'Astros, L.: Les hydrocéphalies, Paris, G. Steinheil, 1898.

De Lange [6] also showed an inclination to the view that the closure of the aqueduct is a developmental anomaly due to a fetal inflammatory process. Guthrie,[3] reporting eight cases of obliteration of the iter, expressed the belief that the defect is due to intra-uterine meningitis of syphilitic, tuberculous or some other origin. Merle [11] ascribed closure of the aqueduct to fetal ependymitis. Dandy [5] expressed the belief that the fetal ependyma is primarily injured either by intra-uterine inflammation or by a toxic or traumatic process and that the injury is healed by glial proliferation. He said that he considered the glial reaction as analogous to that of connective tissue, regarding its growth as secondary and not primary. Schlapp and Gere [4] attributed the proliferation of glia cells to a stimulation by some irritating factor, such as toxic by-products of metabolism.

2. *A Developmental Error, not Due to an Intra-Uterine Inflammatory Process.*—Kernohan [7] stated as his opinion that "during the process of normal fetal development the aqueduct is at first relatively large, but later becomes narrow and this process may go too far." He compared this process to that of the closing of the central canal of the cord, which is not secondary to inflammation.

In our first case, that of a child aged 2 days, there was beginning proliferation of subependymal glia in the form of a projection into the aqueduct. There was no evidence of inflammation either in the subependymal zone or in the meninges or elsewhere in the brain. Since this proliferation of subependymal glia occurred during intra-uterine life in the absence of an inflammatory process, the explanation of the proliferation on the basis of fetal ependymitis or meningitis cannot apply. Nor can Kernohan's theory of exaggerated narrowing of the iter explain the segregated glial proliferation in the present instance. The same can be said of our other five cases, in which the same principle was entailed and in which there was a difference only in the degree of proliferation of the glia cells.

During the course of normal development of the central nervous system the cells that make up the brain tissue make their appearance as undifferentiated cells close to the ependyma. Adjacent to the ependymal layer is the mantle layer, in which the undifferentiated cells differentiate into neuroblasts and spongioblasts. These cells actively proliferate in the mantle layer and migrate toward the periphery (the marginal layer). It is reasonable to conceive of the possibility that in the process of proliferation and migration some cells fail to migrate. These cells, instead of wandering toward the periphery (the marginal layer), may in the course of proliferation be dislodged or even actively

11. Merle, P.: Etude sur les épendymites cérébrales, Thèse de Paris, no. 305, 1910.

migrate toward the ependymal layer. The proliferation of cells in the ependymal layer interrupts and pushes the ependyma aside. Some ependymal cells may become entangled in the proliferating cellular mass, which feature is well demonstrated in our first case. The glial proliferation seen in our cases may, therefore, be interpreted as a developmental error caused by the abnormal proliferation and behavior of embryonal cells. In this connection it is interesting to mention that all our patients showed one or more additional developmental anomalies, including spina bifida with meningocele or meningomyelocele, clubfoot, webbing and misdirection of the toes and a bifid ureter. The combination of developmental abnormalities in the central nervous system with anomalies in other organs is further proof of the concept that aqueductal atresia is a form of malformation.

CORTICAL ENCEPHALOMALACIA IN INFANCY

A CONTRIBUTION TO THE STUDY OF INFANTILE CEREBRAL PARALYSIS

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The cerebral palsies of childhood have been intensively studied clinically and have been divided into a number of fairly characteristic categories.[1] Knowledge of the pathology of this group of common neurologic conditions has not kept pace with clinical studies. Very few patients die in the acute stages of the disease. Most of the material obtained at necropsy therefore consists rather of the scars than of the causal lesions. Analysis of the changes observed has failed to produce a clear conception of the pathologic basis of the condition, its etiology and pathogenesis.

Since the address of Strümpell[2] before the German Society of Naturalists and Physicians in 1884, the concept of acute encephalitis in early childhood as a common cause of infantile cerebral paralysis has been received with wide interest in neurologic and pediatric circles. Strümpell noted a close analogy of the condition to infantile spinal paralysis, both being acute illnesses with symptoms indicative of localization in the gray matter of the cerebrum and of the spinal cord, respectively. He therefore applied the term acute polio-encephalitis to the former condition and surmised that possibly both were due to the same noxious (infectious?) agent.[3] Unfortunately, clear pathologic

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1. (*a*) Freud, S.: Die infantile Cerebrallähmung, in Nothnagel, C. W. H.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1897, vol. 9, pt. 3. (*b*) Collier, J. S.: Cerebral Diplegia, Brain **22**:373, 1899; The Pathogenesis of Cerebral Diplegia, ibid. **47**:1, 1924.

2. Strümpell, A.: Ueber die acute Encephalitis der Kinder (Poliencephalitis acuta, cerebral Kinderlähmung), Jahrb. f. Kinderh. **22**:173, 1884.

3. Although it is now thought that an encephalitic form of Heine-Medin's disease may occur, its diagnosis is exceedingly difficult. Bacteriologic or immunologic proof of cases in human beings has never been made (Neal, J. B.: Symptomatology, in Poliomyelitis: A Survey Made Possible by a Grant from the International Committee for the Study of Infantile Paralysis, Organized by Jeremiah Milbank, Baltimore, Williams & Wilkins Company, 1932, chap. 4), and anatomic evidence is not certain.

confirmation of this clinical concept has not been forthcoming. The few patients who have died during acute stages of the illness showed on postmortem examination conditions other than inflammation.

An alternative theory of vascular obstruction has arisen, but opinions have differed somewhat regarding the type of lesion and the structures involved. Major cerebral defects, from either hemorrhage or softening, may be considered as clearly due to gross vascular lesions. Large areas of softening are usually found to be the result of arterial thrombosis, although at times the presence of a source for embolism suggests the latter mechanism.[4] In perhaps the majority of cases the pathologic changes are not so obvious, consisting rather of general or focal cortical degeneration. Gowers[5] assumed that in this type of case superficial venous thrombosis is an important cause of the lesions. Further studies, however, failed to confirm this view except in a few scattered instances. Study of the arterial tree has been more fruitful. A number of cases are to be discussed in this paper in which lesions of the cerebral arteries, at times with actual occlusion, have been found associated with focal degeneration of the cerebral cortex. More commonly one finds diffuse changes in the cortex, particularly loss of ganglion cells (Collier[1b]) and gliosis. They are at first sight of a different nature from the focal lesions just mentioned. It may be possible, however, that the diffuse changes in the cerebral cortex of infants are caused by a more general disturbance of the cerebral circulation. Such an alteration has been studied in a variety of disorders in adults and is believed to be due to vasomotor disturbances in the brain (Spielmeyer[6] and others).

I wish to report a clinicopathologic study of the case of an infant with convulsive attacks and hemiplegia. At necropsy, multiple areas of encephalomalacia were seen, limited to the cerebral cortex. Definite arterial lesions were present, but they were not sufficiently severe to be alone responsible for the parenchymatous lesions. The condition was similar in many respects to that in other cases recently described and represents, I think, a not uncommon pathologic basis for infantile cerebral paralysis.

REPORT OF A CASE

CASE 1.—B. B., a girl aged 9 months, was born spontaneously at term, labor lasting four days. At first she cried incessantly until phenobarbital was given, which offered relief. The dose of this drug was then decreased. She appeared

4. Heubner: Ueber cerebrale Kinderlähmung, Wien. med. Bl. **6**:373, 1883; cited by Freud.[1a]

5. Gowers, W. R.: A Manual of Diseases of the Nervous System, London, J. & A. Churchill, 1888, vol. 2.

6. Spielmeyer, W.: Zur Pathogenese örtlich elektiver Gehirnveränderungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:756, 1925.

well until in November 1933, at the age of 4 months, she had a convulsion, localized to the right side of the face. Several days later the attack recurred and spread successively to the right upper and lower extremities, being then followed by loss of consciousness for three or four minutes. Later in the day a similar convulsion occurred. At that time there was no postconvulsive paralysis. The dose of phenobarbital was increased temporarily, but as no further attacks occurred for three months, the medication was gradually discontinued. However, she did not regain her former strength, and on March 26, 1934, she had another convulsion. This time the pattern had changed, there being clonic movements of the left hand and arm without any observed spread. A physician was summoned, who noted a left hemiplegia and hemianesthesia, with loss of the deep reflexes in the affected extremities. The reflexes soon returned, but the paralysis persisted, and the child became unresponsive. Her appetite was poor, but she did not vomit. There was at times a moderate fever, the temperature being as high as 39 C. (102.2 F.) She was seen by Dr. John L. Garvey, of Milwaukee, who referred her to the University of Chicago Clinics, where she was admitted on April 3, 1934. She had had none of the ordinary infectious diseases. No other members of her family had had convulsive seizures.

Examination showed an undernourished child. The head was not enlarged, and there was no definite cracked-pot sound on percussion. The fontanel was small and flat. A general physical survey revealed only a barely palpable liver and some tenderness in the left costovertebral angle. Neurologic examination revealed a left spastic hemiplegia and also slight spasticity of the right leg. Ocular movements to the left seemed limited, but the pupils and fundi were normal. There was no demonstrable sensory defect. The tendon reflexes were exaggerated on the left side and to a less extent in the right leg. The abdominal reflexes were weak. The plantar response was flexor on both sides. The neck was not stiff.

The urine contained a trace of albumin and was loaded with pus cells. The leukocyte count of the blood was 6,000, and the red cells numbered 4,700,000.

On the day after admission trephination was performed on both parietal regions for possible subdural hematoma. On the right side the dura mater appeared dark, but no clot was found beneath it. On the left side also the dura mater looked dark. When it was opened, a considerable amount of dark bloody fluid spurted forth, so much so that it was at first thought that a vein or a dural sinus had been cut. After about an ounce of this fluid had escaped, a large cavity could be seen in the superior parietal region. This was irrigated, and the wound was closed with drainage. After the operation the patient's condition was poor. Despite stimulants and transfusion of blood, circulatory and respiratory failure set in, and she died six hours after operation.

Gross Observations at Autopsy.—Examination was limited to the head and performed thirteen hours after death. A small amount of clotted blood was found beneath each operative defect in the dura mater. The blood could be separated easily from the dura, revealing no discoloration of this membrane. A mild microgyria was possibly present. The leptomeninges showed a moderate diffuse thickening. There was a localized collection of blood in the subarachnoid space over each parietal region. On transverse section through this region the cerebral cortex appeared hyperemic. Careful examination of the rest of the brain showed numerous other areas in which the cortex appeared vascular and in places softened and slightly yellow. These changes were most pronounced in the parietal lobes. The vessels of the subcortical white matter were somewhat dilated. In the subcortical substance of the right parietal lobe there was a sharply circum-

scribed bright yellow area, about 1 by 4 mm. in size. The basilar artery was of normal size, but on section the wall seemed excessively thick and the lumen narrow. The circle of Willis was of normal configuration; the arteries forming it were also thickened but patent.

Microscopic Examination.—Cerebral Cortex: The relatively uninvolved cerebral cortex (fig. 1) showed certain diffuse changes of the ganglion cells. These changes were most marked in the third layer of Brodmann. Here the ganglion cells were decreased in number. Most of the cells of this layer were enlarged and had undergone a severe hydropic change; there was considerable cytoplasmic vacuolation and separation of the cell boundaries (fig. 2). The Nissl substance was finely granular and pale. The nuclei were darker than normal, being not infrequently darker than the cytoplasm. They, however, were not pyknotic. There were frequent small areas of absence of ganglion cells from

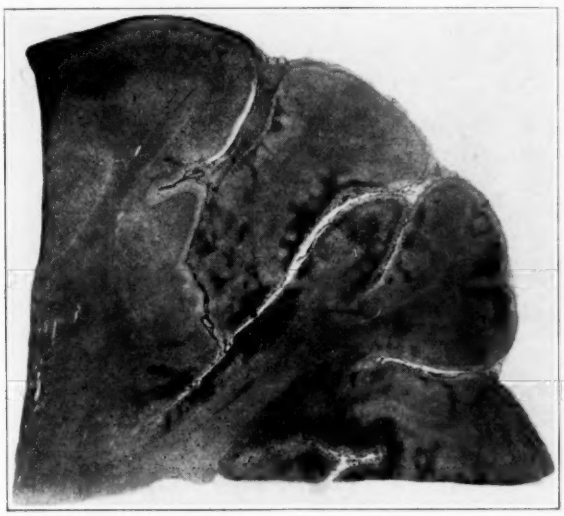

Fig. 1.—General view of a section through the right parietal lobe, showing lesions limited to the cerebral cortex, compared with the relatively normal cortex on the left side. Hematoxylin stain; × 3.

lamina III, as will be noted later. The cells of the other layers showed lesser degrees of these changes. A few of the cells showed the same cytoplasmic picture; the nucleus frequently appeared somewhat dark. The Nissl granules in the deeper layers were in general fairly well preserved. There was nowhere a pronounced satellitosis.

Impregnations made by Bielschowsky's method showed an irregular granulation of the cytoplasm of the ganglion cells, the granules being of various sizes and tending to be arranged peripherally, so that the perinuclear zone was fairly clear. No definite intracellular neurofibrillae were demonstrated. The nerve fibers at a distance from the cells, both in the cortex and in the white matter, showed, however, no definite alteration, distinct fibrillae being in places impregnated. The astrocytes were slightly, diffusely increased; in the subpial layer

they were numerous, enlarged and cytoplasmic; they showed a few fine granules in thionine preparations. The microglia and oligodendroglia did not appear altered in these relatively uninvolved portions of the cortex, and the vessels also appeared normal.

Subcortical White Matter: Throughout the subcortex there were scattered ganglion cells undergoing changes similar to those of the cortical cells. The number of astrocytes and oligodendroglia cells was moderately increased. The larger blood vessels showed fairly marked dilatation and engorgement. The capillary bed, however, appeared normal. There were widely scattered granules, usually lamellated, of a calcium-like material, staining light bluish green with thionine and darker blue with hematoxylin; these usually were adjacent to or in the adventitia of blood vessels.

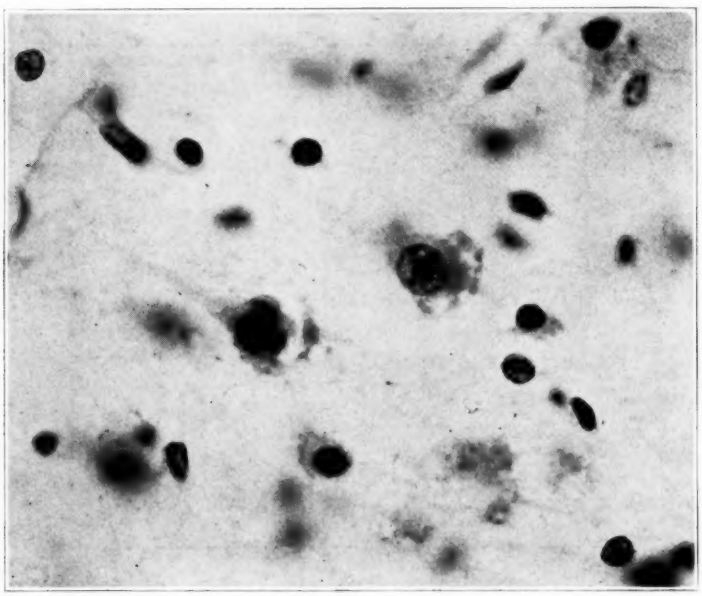

Fig. 2.—Ganglion cells of lamina III in the relatively little affected cortex. Vacuolation and disruption of the peripheral cytoplasm may be seen, with darkening of the nucleus. Thionine stain; × 700.

Cortical Lesions: In all lobes of both cerebral hemispheres there were innumerable sharply defined lesions limited to the cortex, having characteristics as follows (fig. 1): They varied in size from less than 1 to 5 mm. in diameter and tended to form in groups. Smaller lesions and the margins of larger ones were usually confined to layers II and III of the cortex, the bulk of the larger ones extending deep into layer VI but never beneath this into the subcortical white substance. The most striking feature of all the lesions was their extensive vascularity, well shown in Perdrau preparations (fig. 3). There was marked proliferation of capillaries; these as well as medium-sized vessels were engorged with blood. Their walls contained, as seen in connective tissue impregnations, almost invariably only a single layer of reticulin.

The picture was different, however, in the Nissl preparations (figs. 4 and 5). In these, in the active lesion, each blood vessel was shown to contain, in addition to its endothelial lining, one or two other layers of cells. The endothelial cells of the larger vessels were flattened, but those of the capillaries usually were rather rounded and often were of such size as almost to occlude the lumen. The nuclei of the endothelial cells were very large, half as wide as they were long, slightly wrinkled in outline and vesicular, with several small granules of chromatin. The endothelial cytoplasm stained slightly with thionine.

The cells surrounding the endothelium varied in their structure. Many resembled closely the endothelial cells, having identical nuclei (fig. 6); these

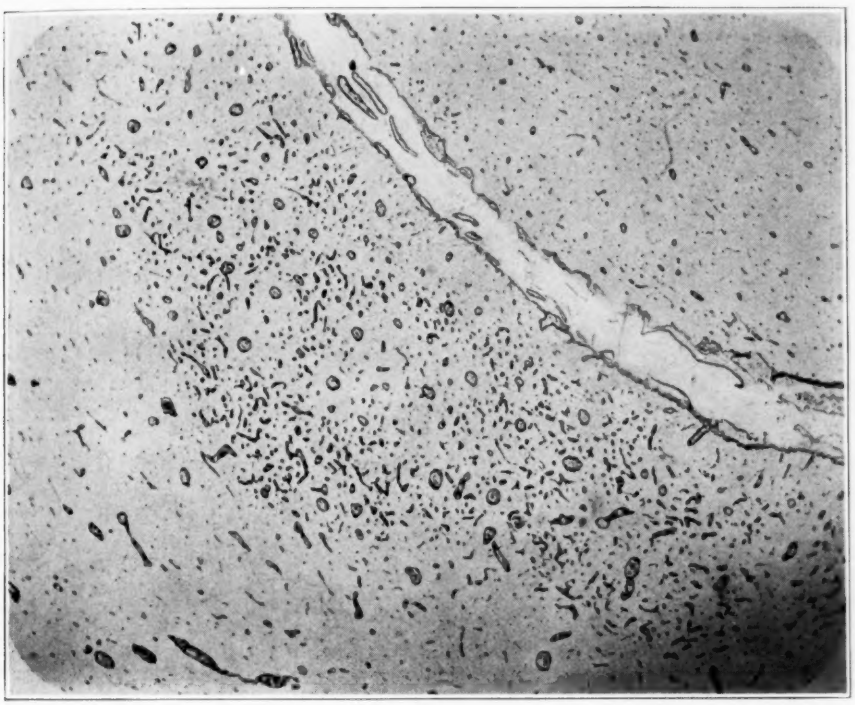

Fig. 3.—Connective tissue stain of a cortical lesion. Note the intense vascular proliferation. Perdrau's method; × 27.

corresponded to the "adventitial cells" of Marchand. In other cells the nuclei were similar in structure to the endothelial nuclei but were more nearly round or kidney-shaped. The cytoplasm of these cells was denser and either formed short, stubby processes at the poles of the nucleus or was oval without processes (fig. 5). In these cells the cytoplasm stained darkly, very much like that of a plasma cell, although the nucleus had none of the well known characteristics of such a cell. When the perivascular cells were numerous and formed at least a double layer about the endothelium, the larger and more nearly round cells were placed peripheral to the elongated ones (fig. 5). No mitoses were seen in the perivascular cells. The cytoplasm of some cells was almost homogeneous, but usually

it contained a few minute granules or vacuoles. In only a small number of the perivascular cells was the cytoplasm entirely vacuolated. This agreed with the observation on preparations stained with scarlet red that few of these cells contained more than a small amount of lipoid material (fig. 6). The fat-containing cells were confined to the outermost layers. In addition, there were a few droplets of fat in some cells of all the types described, including those of the endothelium. Staining by Penfield's method impregnated the perivascular cells, which appeared by this method very much as they did in the Nissl preparations; they were either spindle-shaped or fairly well rounded. In only a few lesions could one see lymphocytes in the perivascular spaces, and even in those they were scanty.

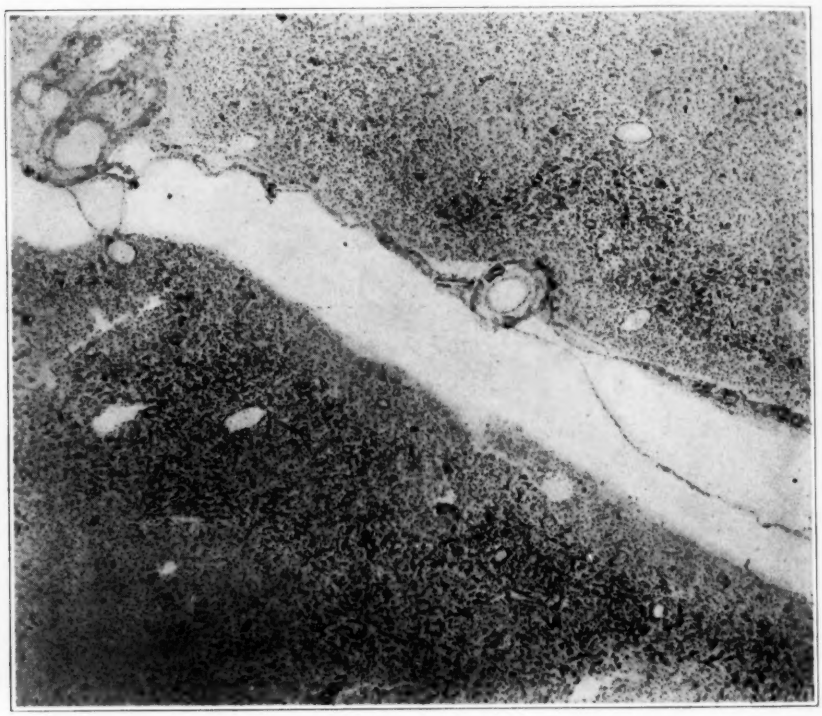

Fig. 4.—Low power photomicrograph of a group of cortical lesions. Note the pale appearance of the calcification of the media of the pial vessel in the center of the photograph. Thionine stain; × 31.

In the active lesions the intervascular spaces were filled rather densely with large numbers of pleomorphic cells. Stained with thionine, the cells appeared as follows: The nuclei for the most part were medium-sized or large and moderately vesicular; they were usually oval, some tending to be kidney-shaped. Their cytoplasm was rather voluminous, stained metachromatically and was either partly or diffusely granular. At times distinct large vacuoles were present. The cells were usually rounded or oval, but in some, particularly at the periphery of a lesion, processes were faintly discernible. Some of the cells were binucleated. Mitoses were not rare (fig. 7); in such dividing cells the cytoplasm tended to be

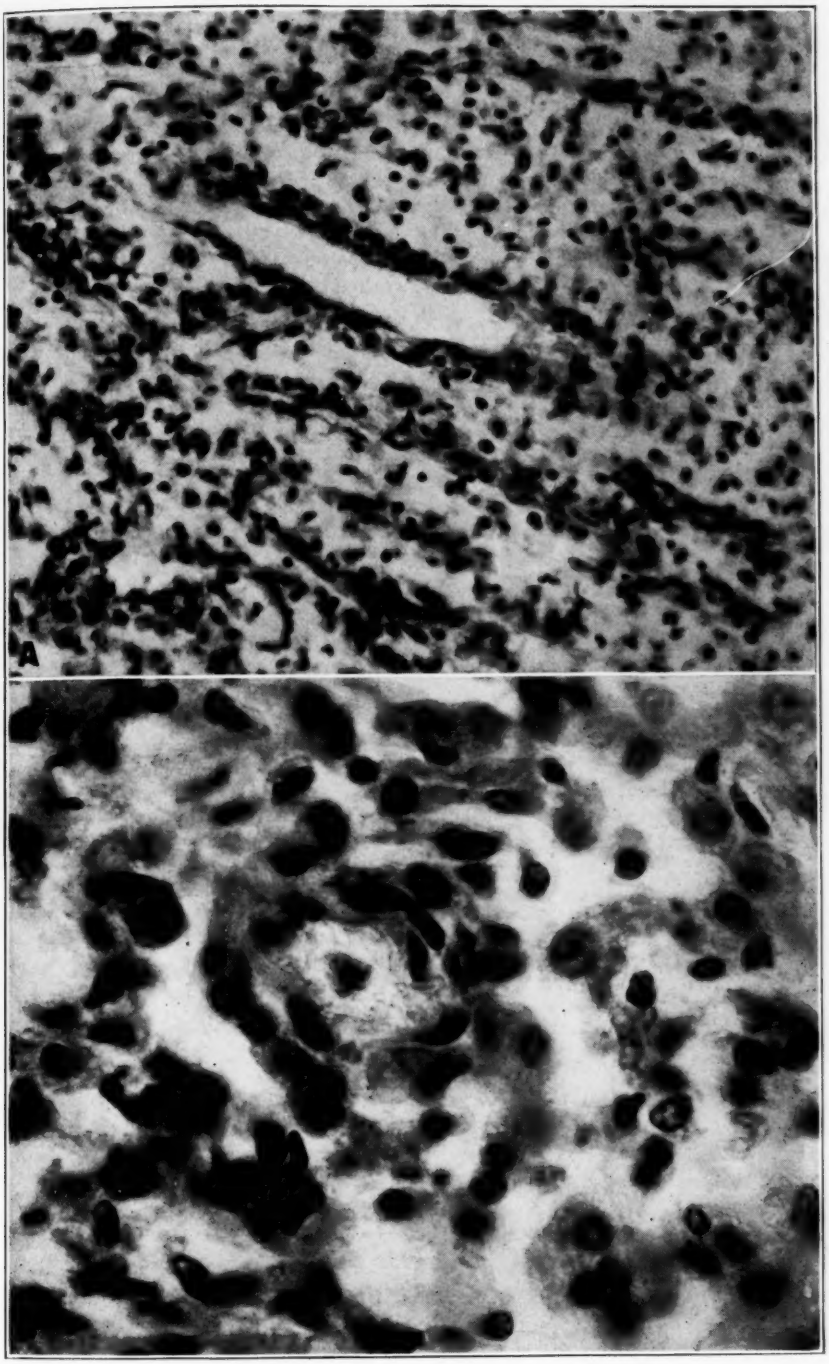

Fig. 5.—Perivascular cells in preparations made by Nissl's method. Stained with thionine *A*; × 290; *B*; × 950.

more homogeneous and deeper staining than in others. There was not infrequently a nuclear process which appeared to be related to numerous filamentous structures which were composed evidently of nuclear material, but without any discernible cytoplasm about them. These structures were usually tortuous and had bulbous thickenings at either end; rarely a small branch could be seen near one end.

This group of rather large cells was readily and specifically impregnated by Penfield's combined method for microglia and oligodendroglia cells. By this technic the cells were shown to be ameboid, almost all possessing processes of varying length and number (fig. 8). The length of some of the processes was amazing, being at least ten times that of a large endothelial nucleus. Six or

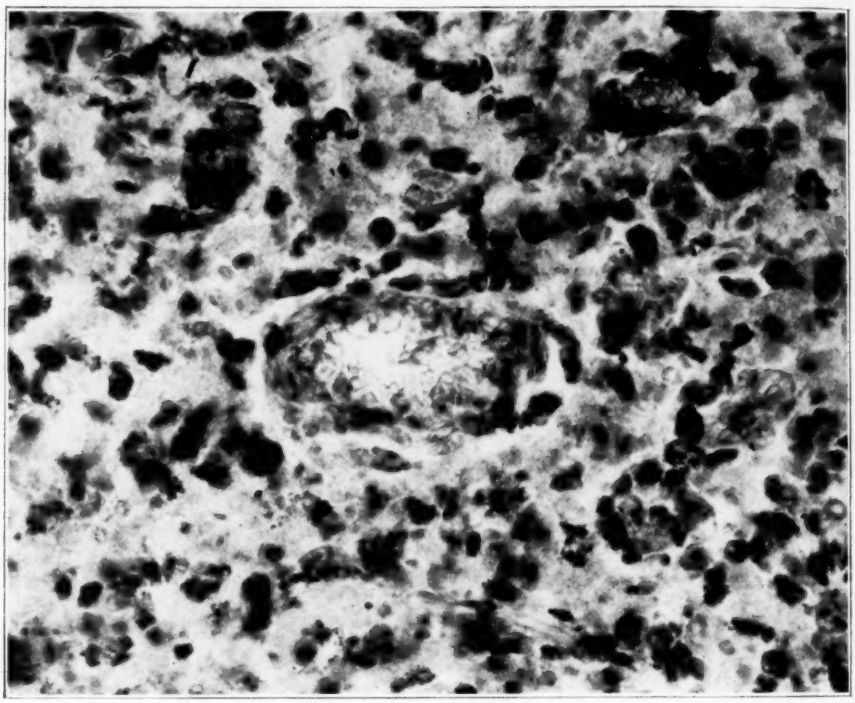

Fig. 6.—Preparation stained for fat. This shows fat-laden cells scattered about, with little tendency to accumulate about the blood vessels. In the wall of the vessel there is below a cell with an elongated, vesicular nucleus, just outside the endothelial cell, which it resembles closely. This is an "adventitial cell" of Marchand. Herxheimer's scarlet red method; × 420.

eight processes directly attached to the body of a cell were not unusual. The processes were blunt, and side branches were few. The cytoplasm of the cells was uniformly, densely granular, except for the presence of vacuoles which were usually small and numerous and gave a reticulated appearance to the cytoplasm. Some vacuoles were large and occasionally contained large, irregular or rounded bodies. A small number of these cells approached a round shape, with few stubby processes. Not infrequently there were what appeared to be two cell

bodies connected by a long narrow bridge of cytoplasm, each of the bodies having its own nucleus; occasionally one of the nuclei appeared to enter the bridge in a manner resembling the extrusion of nuclear processes already noted. These appearances persisted when viewed with the oil immersion objective; they may have been artefacts. The nuclei of the cells showed features similar to those noted in the sections prepared by Nissl's method; in some cells, especially those not vacuolated, they occupied half the entire cell. Some fairly normal-appearing microglia cells could be seen at the periphery of the lesions; these were moderately enlarged and had short spinous processes. By Herxheimer's method the ameboid and globoid cells were shown to be for the most part packed with fat granules. Only in lesions undergoing severe degenerative change did one note accumulation of adiposogranular cells in the perivascular spaces.

Within a cortical lesion there was an occasional large vesicular nucleus with a prominent nucleolus, but otherwise there was no sign of persistent ganglion

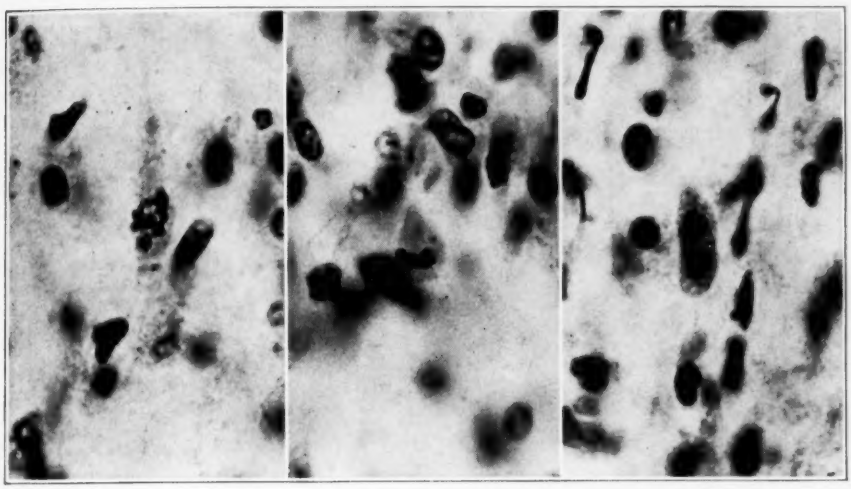

Fig. 7.—Various stages of mitosis occurring in intervascular cells. Thionine stain; × 950.

cells within these foci of softening. Practically no astrocytes could be demonstrated either by Hortega's lithium-silver carbonate method or by Globus' modification of Cajal's gold chloride and mercury bichloride method, except at the margin of the lesion, where large, fibrous astrocytes were present. In addition, in the subpial layer of the cortex overlying a lesion there was pronounced gliosis. The number of microglia cells was moderately increased, and there was a small number of fat-laden cells. Fibroblasts could not be recognized with certainty, but in preparations made either by Perdrau's or by Klarfeld-Achucarro's method, delicate strands of reticulin were observed in places between blood vessels. The amount of intervascular connective tissue was correlated with the intensity of the degenerative processes.

In the tissue surrounding this average lesion the following changes occurred: The alteration of ganglion cells described previously became more marked, the

cells smaller, the nuclei denser and the cytoplasm fainter. The blood vessels were dilated, and their endothelial lining appeared perhaps more cellular. Scattered macrophages were seen; these were shown to be filled with fat when stained with scarlet red. The astrocytes showed a pronounced progressive alteration, both in the cortex surrounding the lesion and in the white substance.

Variant Cortical Lesions: In some areas, occurring either as a part of a typical lesion or separately, the degenerative process was intense, so that when the section was stained for fat it was noted that an extremely dense aggregation of macrophages filled with neutral fat was present. These cells were so closely applied to one another that there was no tissue substance between them. Such lesions were rather small. Near this type of lesion the perivascular spaces were

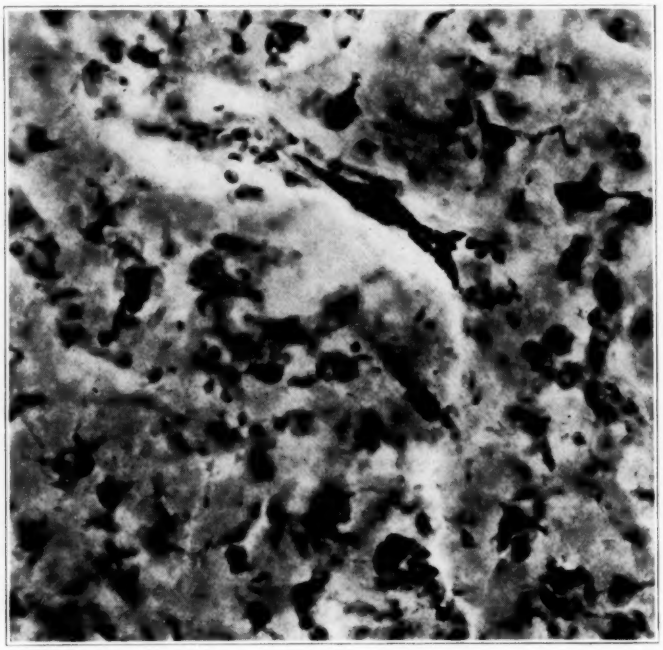

Fig. 8.—Impregnation of intervascular phagocytic cells. Penfield's sodium carbonate-silver method; × 350.

filled with fat-laden corpuscles. An area of complete softening stained by the Globus-Cajal method (fig. 9) showed a center of aurophilic débris within a feebly staining area and surrounded by typical cortical softening on either side and gliosed subcortex beneath.

Another section appeared to show a later stage of the typical lesion that has been described. There was what resembled a skeleton of the typical lesion (fig. 10). Capillaries sprouted in all directions, but their walls were thin and were formed for the most part by the endothelium alone, without the coverings of the perivascular cells. The endothelium was distinctly more cellular than that in vessels in the relatively normal cortex, and its cytoplasm stained much more deeply. A small number of perivascular cells, mainly elongated, were present.

The connective tissue of the vessels was perhaps heavier in this section, but it remained for the most part a single layer. Here and there in the larger vessels the layer of reticulin was reduplicated. The ground substance in this region stained a uniform greenish blue with thionine. In the intervascular spaces there were few cells. These were mostly small cells resembling slightly enlarged microglia, with numerous well staining branching processes. The processes were vacuolated only here and there. These cells were uniformly distributed and possessed no tendency to be related to those of the blood vessels. In addition, there were the filamentous nuclear threads noted previously and many pale blue, dull-staining, naked nuclei, oval or pear-shaped.

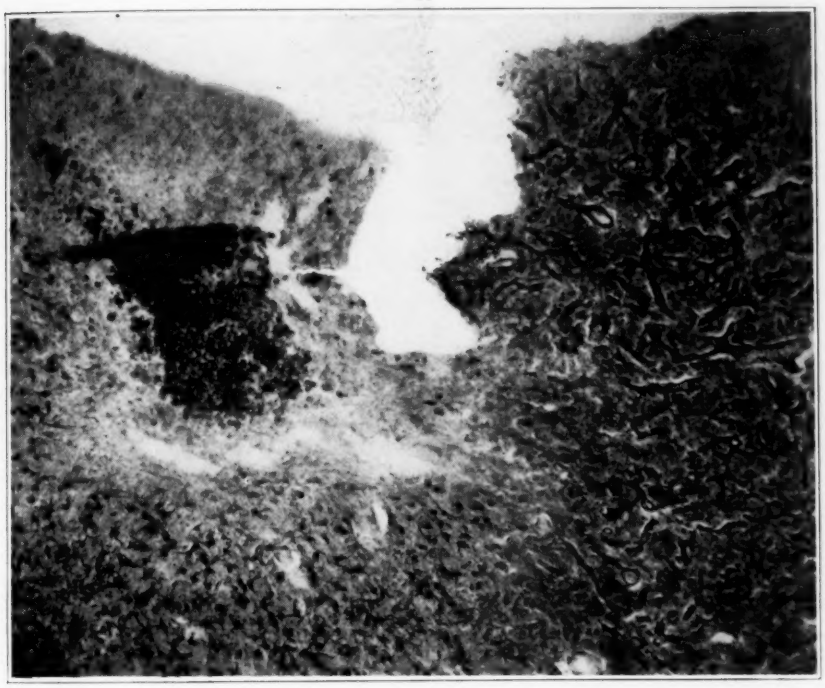

Fig. 9.—Area of complete softening containing aurophilic débris in the center. On the right is a cortical softening, in which the capillary proliferation is well seen. Below are progressively altered astrocytes in the subcortex. Globus's modification of Cajal's method; × 60.

A few areas were noted in the cortex in which the tissue was rarefied, particularly in the middle layers (fig. 11). In addition to this loose glial appearance of the tissue, the blood vessels appeared moderately increased. In the meshes of the cortex there were areas of calcification. These consisted of clumps of minute granules, usually of bizarre shapes, some of a form suggestive of microglia cells. There was no gross formation of cavities. These lesions appeared to represent a late stage in the process of cortical degeneration, forming a status spongiosus.

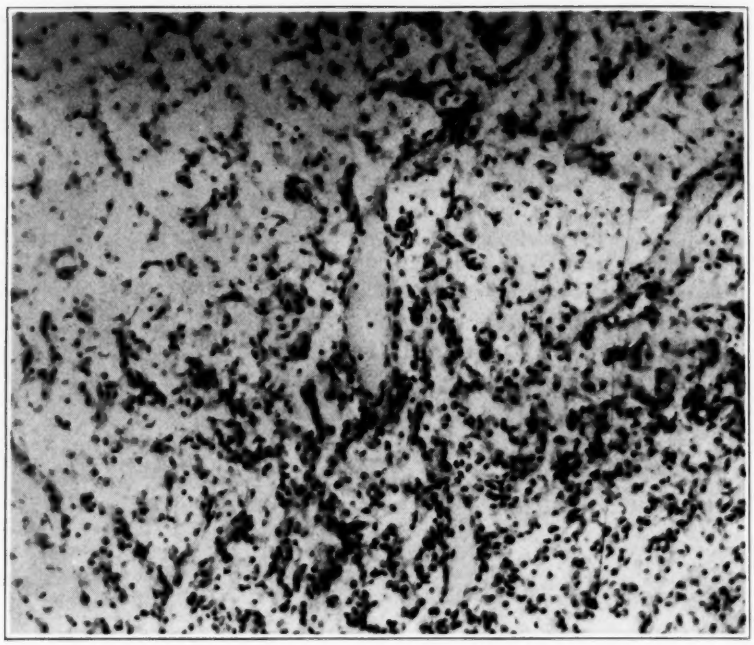

Fig. 10.—Margin of an older lesion. From the upper half most of the mobile elements have disappeared, leaving a skeleton-like tangle of capillaries. The lower half is more cellular and is undergoing active softening. Thionine stain; × 150.

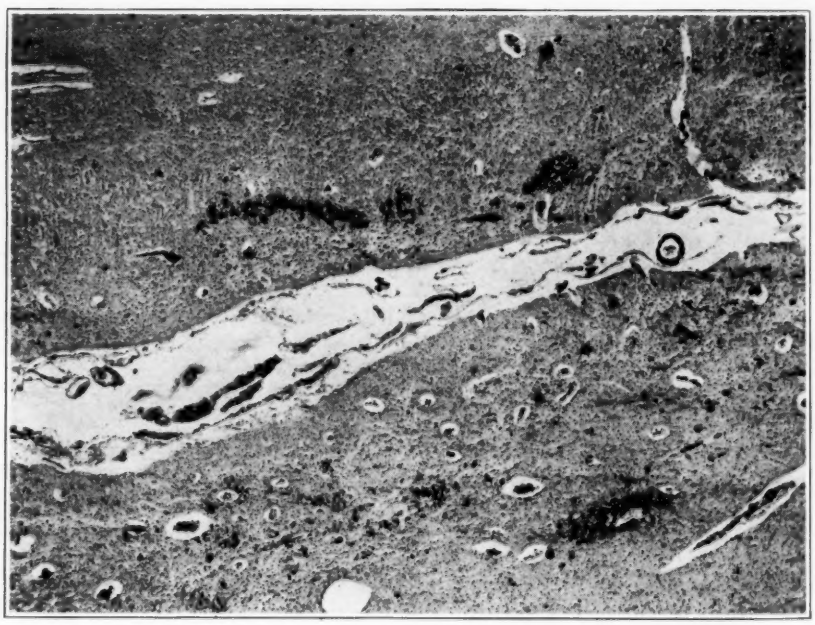

Fig. 11.—Cortical lesions evidently undergoing healing, with rarefied glial tissue (status spongiosus) and granular calcification somewhat resembling microglia cells in shape. Hematoxylin and eosin stain; × 32.

A number of narrow and radially disposed lesions were seen in the cerebral cortex (fig. 12). They extended usually from the superficial layer of the cortex down into the fifth or sixth layer. They were composed chiefly of astrocytes and their fibers (arranged radially), a variable number of hypertrophied microglia cells and in places "calcified" ganglion cells (fig. 13). The latter cells had the characteristic angular shape of ganglion cells and appeared shrunken. There was a clear, oval space in the center representing the nucleus; otherwise the cell was filled with irregular granules of a substance that stained a very faint blue with thionine and dark blue with hematoxylin. In some regions the processes of the cells could be followed for considerable distance; this has been compared by Nissl to the picture of a ganglion cell when impregnated by Golgi's method. The

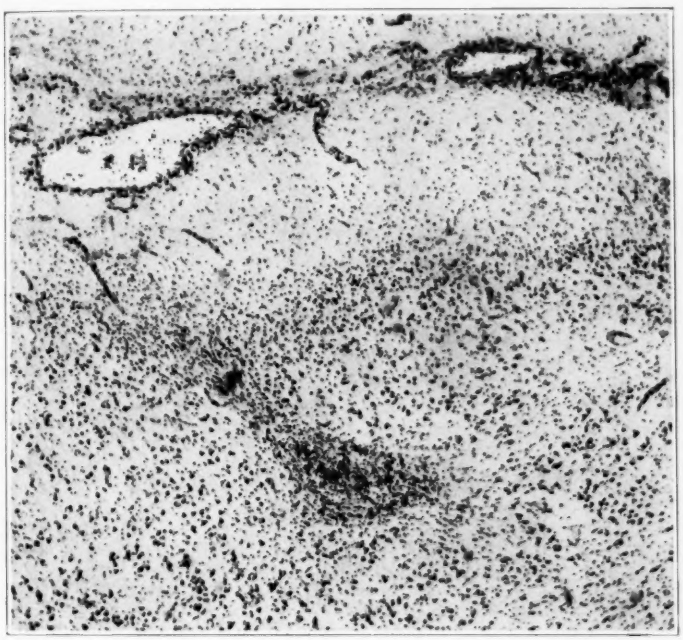

Fig. 12.—Small cortical lesions. In the left side of the photomicrograph there is a radial lesion consisting mainly of astrocytes: Alzheimer's perivascular gliosis. On the right is an earlier stage of this process seen on cross-section; here one sees only absence of ganglion cells: *Verödungsherd.* Thionine stain; × 55.

lesions resembled in many respects those seen in arteriosclerotic disease of the brain and termed by Alzheimer "perivascular sclerosis." Another alteration of the cortex, probably related to this gliosis, was focal loss of ganglion cells about the blood vessels of the cortex (fig. 12), particularly in the third layer. Numerous lesions of this character *(Verödungsherde)* were seen. In these areas the glia was a little altered. About some of the vessels also calcified ganglion cells were noted.

Changes in the White Matter: The single lesion noted in the gross examination of the subcortical substance was shown by preparations stained with scarlet red to be a focus of rather intense degeneration, being completely filled with fat-laden macrophages. Surrounding this rather sharply defined area of softening

were scattered macrophages filled with fat, and about this for several millimeters were minute granules of lipoid substance about some of the nuclei, resembling those of oligodendroglia cells. The macrophages in this lesion appeared more uniform and round than those noted in the various cortical softenings. The perivascular spaces in the neighborhood were packed with fat granule cells.

In other places accumulations of cells were noted in the white matter, consisting of hypertrophic astrocytes, microglia cells, oligodendroglia cells and some macrophages with vacuolated cytoplasm (as seen in the preparation made by Nissl's method). In addition, numerous small cells were noted, of which the nuclei were approximately the size of the nucleus of an oligodendroglia cell but were denser; no cytoplasm was visible, but surrounding the nucleus were clusters of small

Fig. 13.—"Calcified" ganglion cells at the lower end of the radial scar depicted in figure 12. Hematoxylin stain; × 350.

granules. These areas were not more vascular than the adjacent more normal white matter.

Myelin sheath preparations showed nothing definitely abnormal in the white matter.

The changes here described affected parts of all lobes of both cerebral hemispheres. They were most pronounced, however, in the parietal lobes.

The rest of the brain was practically normal. The cornu ammonis showed only a moderate hyperemia. In the basal ganglia there was an occasional fat-laden macrophage free in the parenchyma. In the perivascular spaces of the basal nuclei, in the thalamus and down as far as the midbrain there were a few such macrophages. The cells of these structures, including those of the substantia nigra, were fairly well preserved and contained no fat granules in preparations stained with scarlet red. The pons and the cerebellum were likewise normal.

Granules of calcium were scattered in the diencephalic structures but were less numerous there than in the white matter and cortex of the cerebrum.

Meninges: The leptomeninges over the convexity of the brain and also at the base were thickened, and their spaces were distended. In the meshes lay numerous cells of various types. Some of these cells had fairly dense nuclei and uniform, rounded cytoplasm; others had more extensive and vacuolated cytoplasm, which was seen to contain fat when stained with scarlet red. Fibroblasts were present and also a few lymphocytes. The blood in the subarachnoid space over both parietal lobes was undergoing disintegration, as shown by the appearance of fine granular pigment in phagocytic cells within the blood and in the adjacent

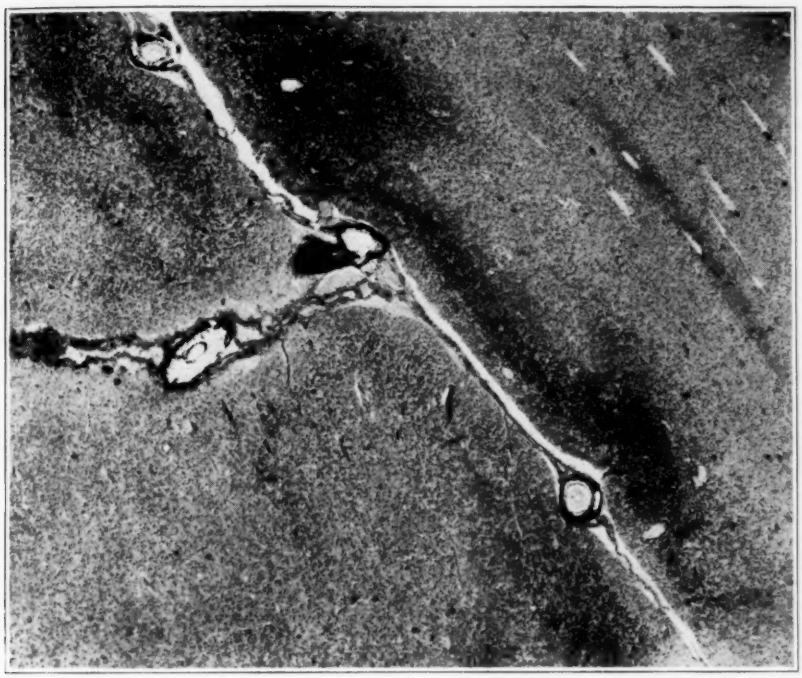

Fig. 14.—Group of pial arteries showing calcification of the media and proliferation of loose intimal connective tissue. The lower left vessel shows also a secondary ring of calcification, and the lumen within this is completely occluded by loose reticulin. Hematoxylin stain; × 20. Compare with the appearance of a pial artery when stained with thionine (fig. 4).

meninges. The dura mater appeared normal except for scattered nodules of calcium.

Blood Vessels: Pronounced and striking changes were noted in the blood vessels, particularly in those of the pia mater. As noted previously, the intracerebral vessels were in all parts of the brain involved by scattered granules of calcium. These granules were rounded and often occurred in clumps, with a lamellated structure. While they occurred also free in the brain tissue, they were more numerous in the adventitia of the intracerebral arteries in both gray

and white matter. In some of these vessels there was a mild proliferation of the adventitia, but changes aside from calcification were mild. The veins were moderately dilated, but their walls appeared normal. In the pial arteries more advanced change had occurred (fig. 14). Some were noted with deposits of a hyalin-like substance in the media and in the inner layers of the adventitia. This substance usually formed a complete ring but was at times interrupted. It stained a glassy pale blue with thionine (fig. 4) and dark blue with hematoxylin (fig. 14). It did not give a reaction for iron when treated with ammonium sulfide or by Turnbull's method. In such vessels the lumen was sometimes wide and the intima normal. In many, however, there was proliferation of the intima, resulting in the formation of a loose network of fine fibrils of reticulin beneath the single layer of endothelial cells. In the meshes of this network of connective tissue lay a few scattered fibroblasts, larger round cells and rounded granules of

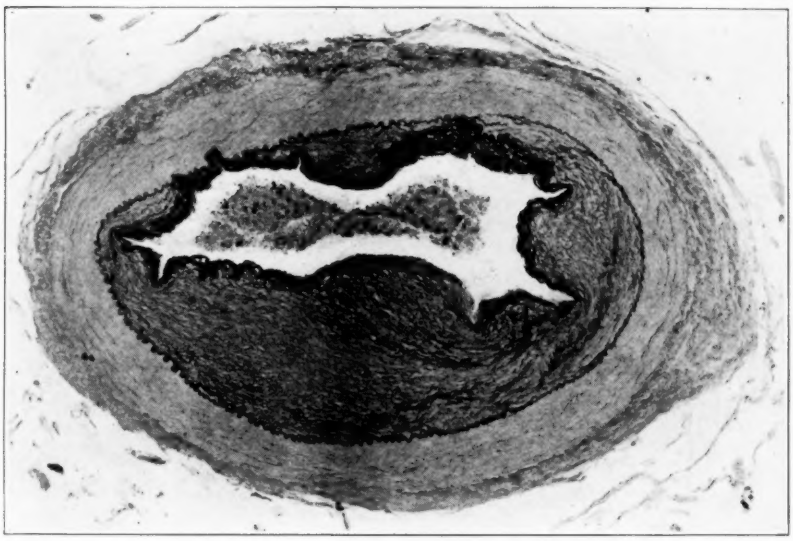

Fig. 15.—Right middle cerebral artery. Elastic tissue preparation, showing slightly split internal elastic membrane and marked intimal proliferation. Weigert's resorcinol-fuchsin stain; × 65.

calcific material. The lumen of a fairly large pial artery was thus sometimes constricted to the size of a large capillary. In one vessel complete occlusion of the lumen had taken place, evidently the result of a two stage process (fig. 14). In this instance there was a ring of calcium-containing material about the margin, with a loose network of reticulin within; about the middle third of the vessel was a secondary ring of similar calcium-containing material. The center of this second ring was entirely filled with the reticulated tissue, there being no lumen. Evidently either thrombosis with complete organization had occurred or the proliferative process alone had resulted in complete obliteration of the vascular lumen. No vessel in the stage of recent thrombosis was seen.

The middle cerebral and basilar arteries showed a pronounced thickening of the intima (fig. 15). The media was quite normal, as was the adventitia. The

internal elastic membrane was split in a few places but was otherwise intact. The thickening of the intima was irregular, giving a nodular appearance. It was fairly cellular. There was an increase in elastic fibrils, most marked immediately beneath the endothelium. In a few small areas the intima stained poorly both with hematoxylin and with resorcinol and fuchsin. Van Gieson's stain disclosed practically no collagen in this layer, and stains for fat likewise gave negative results. The endothelium was intact. There was no evidence of thrombosis.

COMMENT

The lesions in the cerebral cortex were evidently foci of cortical softening, with a definite tendency to be accentuated in certain cell layers, particularly the second and third. Such areas of laminar cortical degeneration have been found in patients of all ages (Probst[7]). They may usually be related directly to alterations in the cerebral circulation. These alterations may be organic, as in arteriosclerosis, but they occur more often in the absence of local occlusive arterial disease, even when the larger vessels show definite structural change. In such instances a functional circulatory insufficiency has been postulated.

Cortical softenings have been described in a variety of disorders in which vasomotor disturbances with asphyxia occur. These lesions are found most commonly associated with arteriosclerosis (Vogt and Vogt,[8] Brinkmann,[9] Spielmeyer,[6] and Neubürger[10]). They have also been described as associated with fat and air embolism (Neubürger,[11]), carbon monoxide poisoning (Hiller,[12] Wilson and Winkelman,[13]), arterial hypertension (Neubürger[14]), epilepsy (Spielmeyer,[6] Hodskins

7. Probst, M.: Ueber durch eigenartigen Rindenschwund bedingten Blödsinn, Arch. f. Psychiat. **36**:762, 1903.

8. Vogt, Cécile, and Vogt, O.: Erkrankungen der Grosshirnrinde im Lichte der Topistik Pathoklise und Pathoarchitektonik, J. f. Psychol. u. Neurol. **28**:1, 1928.

9. Brinkmann, F.: Ueber flächenhafte Rindenerweichungen bei Arteriosklerose der kleinen Rindengefässe, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:182, 1925.

10. Neubürger, K.: Ueber streifenförmige Erkrankungen der Grosshirnrinde bei Arteriosklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:452, 1926.

11. Neubürger, K.: Ueber cerebrale Fett- und Luftembolie (Nebst Bermerkungen zur Frage der Schichterkrankungen der Grosshirnrinde und der Pathogenese der Keuchhusteneklampsie der Kinder), Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:278, 1925.

12. Hiller, F.: Ueber die krankhaften Veränderungen im Zentralnervensystem nach Kohlenoxydvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:594, 1924.

13. Wilson, G., and Winkelman, N. W.: An Unusual Cortical Change in Carbon Monoxid Poisoning, Arch. Neurol. & Psychiat. **13**:191 (Feb.) 1925.

14. Neubürger, K.: Ueber Ammonshornveränderungen bei apoplektischen Hirnblutungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:325, 1927.

and Yakovlev[15]), eclampsia of pregnancy (von Braunmühl,[16] de Vries[17]) and other conditions. One of de Vries' other patients, a soldier, was injured in war and suffered severe traumatic shock, the blood pressure being imperceptible for almost a day. Löwenburg,[18] in Jakob's laboratory, noted a typical cortical softening at a distance from a meningeal tumor.

The nature of the functional circulatory disturbance is a matter of some discussion. Following Ricker,[19] many authors expressed the belief that a primary arteriolar spasm, if prolonged, results in various degrees of stasis with resultant asphyxia of the tissue. Others[10] expressed doubt of the existence of the secondary vascular dilatation of stasis and maintained that prolonged vasoconstriction alone is the essential pathophysiologic process.

Before proceeding to a discussion of cortical encephalomalacia in infancy and early childhood, I shall review the data concerning the arterial lesions and pathologic reactions in the case reported here. In most of the pial arteries over both cerebral hemispheres a marked calcification had taken place in the media. While no actual degenerative changes were to be observed in the other vessels, it may be presumed that this change was the result of necrosis of the media. Proliferation of the intima was present in most of the affected arteries, varying in degree in different vessels. The subendothelial tissue was only moderately cellular. The vessels were thus narrowed, but only one, as noted, was found to be completely occluded. The larger arteries at the base of the brain showed proliferation of the intima, with mild alteration of the internal elastic membrane but no change in the media. The adventitia was normal except for areas of slight thickening in the calcified vessels. There was practically no cellular infiltration of an inflammatory nature. The proliferative endarterial changes observed in the basal arteries resembled closely the compensatory thickening of

15. Hodskins, M. B., and Yakovlev, P. I.: Neurosomatic Deterioration in Epilepsy: A Clinicopathologic Contribution to the Concept, with a Report of Two Cases, Arch. Neurol. & Psychiat. **27**:113 (Jan.) 1932.

16. von Braunmühl, A.: Ueber Gehirnveränderungen bei puerperaler Eklampsie und ihre Enstehung durch Kreislaufstörungen (Zugleich ein Beitrag über weitere akute Kreislaufstörungen am Zentralnervensystem), Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:698, 1928.

17. de Vries, E.: Acute Diseases of the Brain Due to Functional Disturbance of the Circulation: Laminated Cortical Disease, Arch. Neurol. & Psychiat. **25**: 227 (Feb.) 1931.

18. Löwenburg, K., cited by Jakob, A.: Normale und pathologische Anatomie und Histologie des Grosshirns, Vienna, Franz Deuticke, 1927, vol. 2.

19. Ricker, G.: Die Enstehung der pathologisch-anatomischen Befunde nach Hirnerschütterung in Abhängigheit vom Gefässnervensystem des Hirnes, Virchows Arch. f. path. Anat. **226**:180, 1919.

the intima seen when occlusion of distal segments of blood is present. While this may well be the explanation of the changes in the larger arteries, it seems that the thickening of these vessels was relatively much greater than could be accounted for by the narrowing of the arterial bed farther on. The blood vessels of the cerebrum showed otherwise a pronounced distention and were filled with blood. If this may be used as a criterion, one may infer a condition of stasis in the cerebral vessels as the basis for the production of these foci of softening.

The cause of the arterial disease is obscure. Syphilis, while not entirely excluded, seems unlikely in view of the absence of inflammatory reaction. Tests for serologic reactions were unfortunately not made. Infection of the urinary tract might possibly have played a rôle in the pathogenesis of the arterial degeneration. The arteriolar sclerosis was not of the type associated with arterial hypertension, nor did the changes resemble those of periarteritis nodosa.

The pathologic reaction in the cortical lesions in this case was essentially a mesodermal one. First, vascular proliferation was a constant and most intense feature. It was sharply localized to the foci of encephalomalacia and was in fact limited to the laminae actually affected. Thus it spared almost entirely lamina I. In a number of places cell stains or, better, Perdrau's method showed proliferation of capillaries limited to the second layer. This was seen in the large section shown in figure 1.

The second feature of the tissue response is the marked accumulation of phagocytic cells in and about the lesions. The mesodermal nature of these cells has been demonstrated chiefly by the work of del Rio-Hortega [20] and confirmed with the aid of intravital staining (Macklin and Macklin; [21] Russell [22]). The latter authors, in their experiments using trypan blue, showed that macrophages in the brain may be derived from certain cells other than those commonly recognized as the source, the microglia cells. Thus they found that in wounds of the brain the vital dyes are taken up partly by spindle-shaped cells lying in the adventitia of vessels, by swollen endothelial cells and by leptomeningeal elements. The impression derived from examination in the case reported here is in accord with these observations. One of the striking features of the lesions in my case is the accumulation of oval and

20. del Rio-Hortega, P.: Microglia, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, chap. 10.

21. Macklin, C. C., and Macklin, M. T.: A Study of Brain Repair in the Rat by the Use of Trypan Blue, with Special Reference to the Vital Staining of the Macrophages, Arch. Neurol. & Psychiat. **3**:353 (April) 1920.

22. Russell, Dorothy S.: Intravital Staining of Microglia with Trypan Blue, Am. J. Path. **5**:451, 1929.

spindle-shaped cells about the proliferated blood vessels. All stages of transition from these cells into macrophages can readily be traced, indicating their origin from perivascular histiocytes.

The origin of perivascular histiocytes is a matter of dispute. Such cells might conceivably arise: (1) by the proliferation of adventitial histiocytes normally present, (2) by migration of certain elements of the blood (monocytes and lymphocytes) through vessel walls and their accumulation in the perivascular region or (3) by multiplication and transformation of the endothelial cells. All these modes of development might give similar pictures in fixed preparations; so one must rely on the results of controlled experimentation for an answer. A survey of the literature indicates considerable diversity of opinion among hematologists. Suffice it to mention the outstanding views. Maximow [23] held that in the process of inflammation polyblasts are derived from local histiocytes and from the lymphocytes and monocytes of the blood. According to Lewis,[24] macrophages are formed from mononuclear cells of the circulating blood. Sabin, Doan and Cunningham,[25] while affirming the origin of clasmatocytes from endothelium, expressed the belief that in disease they are derived from preexisting clasmatocytes (in addition to the endothelium of certain organs, such as the spleen, which, according to Maximow, is really a layer of histiocytes). Following Mallory,[26] other workers [27] expressed the belief that tissue phagocytes are derived from endothelium. Study of the cellular changes in the encephalomalacic foci in my case rather inclined me to the belief that the proliferating cells are derived from the vascular endothelium, but such reasoning, according to Lewis,[24] is fallacious. He stated that "mononuclears . . . can lodge on capillary walls and by changes in form simulate very closely a condition that might be interpreted as transformation of endothelium, where in reality a transformation of mononuclears is taking place."

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23. Maximow, A. A.: Relation of Blood Cells to Connective Tissues and Endothelium, Physiol. Rev. **4**:533, 1924.

24. Lewis, W. H.: The Transformation of Mononuclear Blood Cells into Macrophages, Epithelioid Cells and Giant Cells, Harvey Lectures, 1925-1926, Baltimore, Williams & Wilkins Company, 1927, p. 77.

25. Sabin, F. R.; Doan, C. A., and Cunningham, R. S.: Discrimination of Two Types of Phagocytic Cells in the Connective Tissues by the Supravital Technique, Contrib. Embryol. **16**:125, 1925.

26. Mallory, F. B.: A Histological Study of Typhoid Fever, J. Exper. Med. **3**:611, 1898.

27. Foot, N. C.: The Endothelial Phagocyte: A Critical Review, Anat. Rec. **30**:15, 1925.

CORTICAL ENCEPHALOMALACIA IN INFANCY AND CHILDHOOD

Under a variety of names there appear in the literature descriptions of cortical softening occurring in infancy and early childhood. These may be arranged to form a series which appears to trace the development of cortical sclerosis with cerebral atrophy from fresh softenings, such as I have observed in my case. A typical active stage of the process has also been described by Alpers,[28] from Jakob's laboratory.

> The child was born normally. After a few weeks she began to cry a good deal and had generalized convulsions. Examination at the age of 3 months showed dilated, fixed pupils and rather active knee jerks. After a cisternal puncture she went into a state of circulatory and respiratory collapse, from which she was revived with the aid of stimulants, only to relapse. She died at the age of 5 months. Microscopic examination of the brain revealed decrease and alteration of the cells of the cerebral cortex, particularly in lamina III. Scattered throughout were areas of increased vascularity, destruction of ganglion cells, moderate formation of fat granule cells and astrocytic gliosis. Similar areas were noted in the basal ganglia and in the pons, and complete softening was present in the thalamus. A plaque of intimal proliferation was seen in a pial artery.

This case bears many resemblances to that which I have reported. In both, the first symptom was excessive crying. Simple operative procedures were followed by severe respiratory and circulatory collapse. The cortical lesions were very similar, the differences, such as the astrocytic and phagocytic responses within the lesions, being dependent to a large extent on the severity of the process. In my case no significant lesions were disclosed in the subcortical nuclear masses. Arterial changes were present in both cases, although they were more extensive in mine.

Such cortical lesions have also been studied by Diamond,[29] Reymond,[30] Freedom and Thomson and Piney.[31] Diamond reported two cases.

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28. Alpers, B. J.: Diffuse Progressive Degeneration of the Gray Matter of the Cerebrum, Arch. Neurol. & Psychiat. **25**:469 (March) 1931.

29. (*a*) Diamond, I. B.: Encephalomalacia in Infants (Virchow's Interstitial Encephalitis), Arch. Neurol. & Psychiat. **31**: 1153 (June) 1934. (*b*) Weil, A., in discussion on Diamond, I. B.: Encephalomalacia in Infants (Virchow's Interstitial Encephalitis), ibid. **32**:676 (Oct.) 1934.

30. Reymond: Ueber Encephalitis diffusa, resp. Polioencephalitis der Kinder, quoted by Wachsmuth, H.: Cerebrale Kinderlähmung und Idiotie, Arch. f. Psychiat. **34**:787, 1901.

31. Freedom: Ueber einen eigenartigen Krankheitsfall des jungendlichen Alters under dem Symptomenbilde einer Littleschen Starre mit Athetose und Idiotie, Zentralbl. f. d. ges. Neurol. u. Psychiat. **46**:196, 1926. Thomson, A. P., and Piney, A.: A Case of Decerebrate Rigidity in an Infant, Associated with Diffuse Softening of the Cerebral Cortex and Calcification of the Cerebral Vessels, Lancet **2**:1105, 1921.

The first was that of a 2 month old girl with prenatal iridocyclitis and multiple areas of softening, with cavitation of the cerebral cortex, extending into the adjacent subcortical white substance. His second case was that of a boy who was normal up to the age of 3½ months, when he began to have generalized convulsions during an attack of diarrhea. There were 190 cells in the cerebrospinal fluid. After death at the age of 4½ months examination showed scattered foci of softening and cavitation limited to the cortex. The blood vessels showed intimal and adventitial thickening. The ganglion cells were reduced in number; in and about them were deposits of calcium.

Diamond interpreted the changes as those of Virchow's interstitial encephalitis. In the discussion of this presentation [29b] it was suggested (Dr. A. Weil) that these conditions are different, Virchow [32] having described diffuse and focal accumulations of fat-laden cells throughout the central white matter of the cerebral hemispheres rather than in the cortex.

A somewhat similar case was reported by Ford and Schaffer [33] as part of a review of the etiologic factors in infantile acquired hemiplegia.

The patient was a boy aged 3 years and 11 months in whom, after an infection of the upper respiratory tract, there developed suddenly generalized convulsions, coma and left hemiplegia. Death ensued on the third day of the cerebral disease, and at autopsy softening was noted in the right frontoparietal cortex. The cause of this softening was thrombosis of the right middle cerebral artery, which showed focal necroses of the media, with disintegration of the elastic membrane. In all the cerebral arteries degeneration of the intima had taken place, with the formation of plaques of connective tissue there and accumulation of fat-laden phagocytic cells. Similar changes, but less severe, were found in the arteries of the viscera.

Softenings of the cerebral cortex may likewise occur in the course of common infectious diseases. This complication has been studied best in pertussis. Thus, Husler and Spatz [34] and Neubürger [11] found cortical degeneration in patients who died of convulsions during the active stage of pertussis. The condition may occur also in the course of convalescence from this disease, as in the case reported by Hiller and Grinker.[35]

The patient was a girl aged 3 years who seemed to be recovering satisfactorily from pertussis when there suddenly developed convulsions, high fever and, a day later, left hemiplegia. She died after seven weeks, and at autopsy laminar cortical

32. Virchow, R.: Zur pathologischen Anatomie des Gehirns: I. Congenitale Encephalitis und Myelitis, Virchows Arch. f. path. Anat. **38**:129, 1867.

33. Ford, F. R., and Schaffer, A. J.: The Etiology of Infantile Acquired Hemiplegia, Arch. Neurol. & Psychiat. **18**:323 (Sept.) 1927.

34. Husler, J., and Spatz, H.: Die "Keuchhusten-Eklampsie." Zur Klinik und pathologischen Anatomie, Ztschr. f. Kinderh. **38**: 428, 1924.

35. Hiller, F., and Grinker, R. R.: Functional Circulatory Disturbances and Organic Obstruction of the Cerebral Blood Vessels, with a Contribution to the Pathology of Pertussis Eclampsia, Arch. Neurol. & Psychiat. **23**:634 (April) 1930.

encephalomalacia was noted. The authors emphasized the importance of functional circulatory disturbances in the pathogenesis of the lesions and compared the changes with those occurring in an adult with endocarditis and embolism of the middle cerebral artery.

Particularly in the older literature, one finds many pathologic reports concerning specimens which appear to be later stages of the process that I have been discussing. One of the earliest, yet one of the most complete, monographs on this subject was written by Cotard [36] in 1868 as a Paris thesis. Discussing a group of cases of cerebral atrophy that he studied under Charcot, he divided the lesions into four groups. These were: 1. *Plaques jaunes,* which he compared to similar lesions in adults resulting from occlusion of arteries, either from embolism or from thrombosis. In one case in which these lesions occurred, he was able to demonstrate the occluded vessel. 2. Cysts and cellular infiltration, which he compared also to processes occurring later in life, the end-stages of hemorrhage and softening. These lesions are more likely to occur deep in the substance of the brain, as contrasted to *plaques jaunes,* which involve primarily the cerebral cortex. 3. Disappearance of nerve tissue. 4. Lobar sclerosis, a condition of atrophy of the brain, which may or may not be associated with the formation of minute cysts indicative of vascular lesions. The atrophy may involve an entire cerebral hemisphere and may further cause atrophy of distant parts of the brain. This effect is particularly well shown in atrophy and sclerosis of the contralateral cerebellar hemisphere. Cotard concluded that the pathologic changes in infantile cerebral paralysis resemble alterations in adults but have in addition certain peculiarities of reaction in infancy, namely, the production of lobar sclerosis and porencephaly.

These findings in atrophic lobar sclerosis have been confirmed by a number of investigators, including Jendrassik and Marie [37] and Kotschetkowa.[38] Kotschetkowa studied microgyria, differentiating a type due to a primary developmental defect from an acquired form. The latter type she associated with destruction of the cortex and the formation there of punctate and horizontal striate cavities. She considered these changes to be the result of thrombosis of numerous minute subcortical arteries.

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36. Cotard, J.: Étude sur l'atrophie cérébrale, Thèse de Paris, no. 207, 1868; cited by Freud.[1a]

37. Jendrassik, E., and Marie, P.: Contribution à l'étude de l'hémiatrophie cérébrale par sclérose lobaire, Arch. de physiol. norm. et path. **5**:51, 1885.

38. Kotschetkowa, L.: Beiträge zur pathologischen Anatomie der Mikrogyrie und der Mikrocephalie, Arch. f. Psychiat. **34**:39, 1901.

The occurrence of hemiplegia with an intact pyramidal tract led Bielschowsky [39] to report two cases of cerebral hemiatrophy. Each patient had an acute illness in early childhood, with fever, convulsions and hemiplegia, following in one instance an attack of measles. Although clinically both showed infantile spastic hemiplegia, with increased reflex activity (the plantar reflexes had not been tested), there was noted at autopsy preservation of the entire pyramidal fiber system. Examination of the motor cortex revealed a marked and selective degeneration of the third cell layer with preservation of the Betz cells. In other parts of the atrophic hemisphere, there was severe degeneration of the entire cerebral cortex except the molecular layer. The hemiplegia was considered to result from interruption of intracortical connections to the uninvolved Betz cells. Similar cases [40] have been reported by Spielmeyer, Jakob and others.

One of the outstanding contributions to the study of porencephaly is the monograph by Kundrat,[41] who studied eighteen cases, including the six of Heschl. He concluded that porencephaly is always due to a destructive process, the result of circulatory disturbances, which occur usually prenatally but also after birth. Less extensive defects, he found, usually lie within the territory of a single artery, most often the middle cerebral. The cortical changes frequently were destruction of nerve elements, new formation of vessels and connective tissue and accumulation of fat granule cells. The vessels were usually patent; in fact, they were often dilated. No trace of thrombosis was seen, but in one instance syphilitic endarteritis was associated with cortical degeneration.

Cavitation in the cortex has been observed in cases of trauma at birth (Schwartz [42]), although grosser subcortical defects are more common, apparently resulting from subependymal hemorrhage from the terminal veins in the walls of the lateral ventricles. Schwartz considered these changes to be brought about by alterations in the intracranial pressure during birth by means of vasomotor disturbances (in accordance with Ricker's conception). Cortical softenings were reported by

39. Bielschowsky, M.: Ueber Hemiplegie bei intakter Pyramidenbahn: Ein Beitrag zur Kenntnis des Schichtungsplanes der Grosshirnrinde, J. f. Psychol. u. Neurol. **22**:225, 1916.

40. (*a*) Spielmeyer, W.: Hemiplegie bei intakter Pyramidenbahn (intrakortikale Hemiplegia), München. med. Wchnschr. **53**:1404, 1906. (*b*) Jakob, A.: Zum Kapitel der paradoxen zerebralen Kinderlähmung, Deutsche Ztschr. f. Nervenh. **68-69**:313, 1921.

41. Kundrat, H.: Die Porencephalie: Eine anatomische Studie, Graz, Leuschner & Lubensky, 1882.

42. Schwartz, P.: Erkrankungen des Zentralnervensystems nach traumatischen Geburtsschädigung: Anatomische Untersuchungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **90**:263, 1924.

Köppen [43] associated with bilateral subdural hematoma in a child who died at the age of 3 months, having had convulsions since birth. Later stages with cortical atrophy were also described in association with pachymeningitis haemorrhagica interna by Stroh [44] and Schob.[45]

The pathologic processes present in these cases would appear to be secondary to circulatory disturbances resulting from acquired structural or functional vascular abnormalities. Cortical degeneration may be associated likewise with true developmental defects of the cerebral blood vessels. In this connection I cite briefly the following case.

Case 2.—B. C., a girl aged 4 years, had been normal, aside from extensive vascular nevi of the skin, until the age of 6 months. At that time, after a febrile illness, with colic and diarrhea, she had a series of convulsions lasting several days, after which she suddenly became paralyzed on the right side of the body. A few weeks later the hemiplegia improved, but the convulsive attacks recurred at varying intervals. When the patient was 4 years old, the hemiplegia returned and persisted after a convulsion. At the same time she became speechless and entirely helpless and failed to recognize members of her family. She was referred to the University of Chicago Clinics from the Children's Memorial Hospital and was admitted on Aug. 13, 1934. No other instances of vascular tumor or convulsions have appeared in the family.

Examination showed extensive port wine stain nevi on both sides of the face, scalp and neck and over the lower part of the back and both lower extremities. The distribution of the latter lesion coincided accurately with the fifth lumbar and all sacral dermatomes. There was hypertrophy of the tissues of the left side of the face. No physical evidence of visceral abnormality was detected. She was uncooperative and neither spoke nor appeared to understand what was said to her. The ocular fundi showed no vascular lesion, but there was a glaucomatous excavation of the left optic disk, and the left pupil was sluggish in its reaction to light. Spastic paralysis of the upper and lower extremities was present, with a typical hemiplegic reflex pattern. There was no demonstrable sensory defect. No cranial bruit was heard.

Roentgenograms of the skull showed four discrete calcified lesions in the left cerebral hemisphere. A small one was noted in the region of the middle of the second frontal gyrus, and the other three were in the superior central and parietal regions. The middle one of the latter group, the largest, was shaped like half a cylinder, and stereoscopic roentgenograms showed it to be about 1 cm. from the skull. It appeared to represent calcification in the crown of a gyrus.

If one did not have the cutaneous nevi to help in the diagnosis one would immediately suspect the condition of falling into the clinical group which Strümpell [2] designated as acute polio-encephalitis of childhood.

43. Köppen, M.: Ueber Gehirnkrankheiten der ersten Lebensperioden, als Beitrag zur Lehre vom Idiotismus, Arch. f. Psychiat. **30**:896, 1898.

44. Stroh, H.: Halbseitige Mikrencephalie durch degenerative Atrophie infolge Pachymeningitis haemorrhagica interna bei Möller-Barlowscher Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:1, 1925.

45. Schob, F.: Pathologische Anatomie der Idiote, in Spielmeyer, W.: Der Anatomie der Psychosen, Berlin, Julius Springer, 1930, pt. 7.

The marked vascular abnormality of the skin, however, makes highly presumptive the diagnosis of a congenital, developmental lesion of the intracranial vessels. This is usually a racemose venous angioma of the meninges (Kalischer,[46] Cushing and Bailey [47]) or of the brain (Wolf and Brock [48]). However, other vascular abnormalities of the brain may be associated with a cutaneous nevus. Thus Kufs [49] described multiple telangiectatic nodules ("cavernomas") in the brain of a man with a nevus of the face and neck.

The intracranial calcification that one sees roentgenographically in patients with these conditions is usually different from that shown by my patient. As was first demonstrated by Parkes Weber,[50] there is often a group of intertwining parallel sinuous lines. This is commonly present in the occipital lobe. Pathologic examination of a patient showing this picture in the roentgenogram was made for the first time by Krabbe.[51] Although the calcification may be in the pial vessels (Cushing and Bailey [47]), Krabbe demonstrated that it might be also within the cerebral cortex. The parallel line effect may be due not to vascular calcification but rather to deposits of calcium in the opposing walls of cerebral sulci. This was confined for the most part to the second and third layers, from which the ganglion cells had disappeared, with replacement by glial fibers. The calcium salts were scattered in the ground substance and not in the cortical vessels. The affected occipital lobe was grossly atrophied, and its leptomeninges were thickened. The pia mater was richly vascularized and somewhat angiomatous over the occipital and temporal lobes. The condition appears, then, to be lobar sclerosis due to laminar cortical degeneration with calcification. The pathologic process seems to be fundamentally similar

46. Kalischer, S.: Ein Fall von Teleangiectasie (Angiom) des Gesichts und der weichen Hirnhaut, Arch. f. Psychiat. **34**:171, 1901.

47. Cushing, H., and Bailey, P.: Tumors Arising from the Blood Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas, Springfield, Ill., Charles C. Thomas, Publisher, 1928.

48. Wolf, A., and Brock, S.: The Pathology of Cerebral Angiomas: A Study of Nine Cases, Bull. Neurol. Inst. New York **4**:144, 1935.

49. Kufs, H.: Ueber heredofamiliäre Angiomatose des Gehirns und der Retina, ihre Beziehungen zueinander und zur Angiomatose der Haut, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:651, 1928.

50. Weber, F. Parkes: Right-Sided Hemi-Hypotrophy Resulting from Right-Sided Congenital Spastic Hemiplegia, with a Morbid Condition of the Left Side of the Brain, Revealed by Radiograms, J. Neurol. & Psychopath. **3**:134, 1922; A Note on the Association of Extensive Haemangiomatous Naevus of the Skin with Cerebral (Meningeal) Haemangioma, Especially Cases of Facial Vascular Naevus with Contralateral Hemiplegia, Proc. Roy. Soc. Med. **22**:431, 1929.

51. Krabbe, K. H.: Facial and Meningeal Angiomatosis Associated with Calcifications of the Brain Cortex: A Clinical and Anatomopathologic Contribution, Arch. Neurol. & Psychiat. **32**:737 (Oct.) 1934.

to the condition of cortical encephalomalacia with which this paper is primarily concerned. Such cerebral atrophy associated with nevi of the meninges has been found also by Cushing,[52] Dürck [53] and Lhermitte and Klarfeld.[54] It may also be inferred from the position of the intracranial calcifications in Parkes Weber's [50] case. Extensive calcification of the affected hemisphere was present in Dürck's case, with deposits in the ground substance of the cortex and white matter, blood vessels and ganglion cells. In this case and in that of Lhermitte and Klarfeld there was crossed cerebellar atrophy similar to that found not infrequently in other forms of cerebral hemiatrophy.

A few words may be said regarding intracerebral calcifications in the more common types of cortical degeneration in infancy. In the first case described here such deposition occurred in several forms: as calcospherites scattered throughout the cerebral cortex and subcortex, mainly in the adventitial spaces; in the media of some of the pial arteries, associated with proliferative changes in the intima, and in ganglion cells about ischemic foci undergoing Alzheimer's perivascular gliosis. A similar condition was described by Bertrand and Altschul [55] as "cystic microcephaly." In this case the pial arteries were affected in a fashion identical to that in my case. There was also extensive cortical calcification in Brodmann's lamina III. Schob [45] referred to other cases of cortical atrophy with calcification, reported by Marchand, Zenoni and Vanzetti. Calcification in the tissue and perivascular spaces, glia and nerve cells has been described in Virchow's interstitial encephalitis by Schmincke.[56]

One may thus interpret on the basis of vascular disturbance the development of atrophic lobar sclerosis of the brain, a common lesion in infantile cerebral palsy. Various degrees of cortical encephalomalacia occur, the changes tending to be distributed in certain layers of the cerebral cortex. Milder degrees of alteration may cause only a loss of ganglion cells with perhaps mild gliosis. Alterations of moderate and more marked degree result in glial scars or in rarefaction varying from a status spongiosus to actual cavitation. The lesions are usually confined to the cerebral cortex and affect the subcortical substance,

52. Cushing, H.: Cases of Spontaneous Intracranial Hemorrhage Associated with Trigeminal Nevi, J. A. M. A. **47**:178 (July 21) 1906.

53. Dürck, H.: Ueber fast totale Verkalkung einer Grosshirnhemisphäre bei einem erwachsenen Individuum, Atti Cong. internaz. d. pat., 1911, p. 238.

54. Lhermitte, J., and Klarfeld, B.: Etude anatomique d'un cas d'atrophie croisée du cervelet, Rev. neurol. **22**:73, 1911; cited by Bertrand and Altschul.[55]

55. Bertrand, I., and Altschul, R.: Le métabolisme cérébral du calcium, Rev. neurol. **2**:241, 1927.

56. Schmincke, A.: Encephalitis interstitialis Virchow mit Gliose und Verkalkung: Zugleich ein Beitrag zur Verkalkung intracerebraler Gefässe, Ztschr. f. d. ges. Neurol. u. Psychiat. **60**:290, 1920.

chiefly by secondary degeneration. More severe lesions may, however, extend deep into the white matter and cause major porencephalic defects. Generalized atrophy or hemiatrophy of the brain may result when the lesions occur early in life.

It seems probable that the lesions are due to deficient circulation. The distribution of the degeneration and its histopathologic features are typical of those found in a variety of circulatory and nutritional disturbances. Organic vascular disease has been noted in many cases but is rarely sufficiently severe to cause by itself ischemia of the cortex. One may postulate, then, functional vascular disturbances. The severity of these vasomotor reactions or the increased susceptibility of the brain, from either systemic intoxication or organic vascular disease, may cause softening of the cortex.

SUMMARY

A case is reported of an infant with convulsive seizures beginning at the age of 4 months and hemiplegia beginning at the age of 9 months. Death occurred in the ninth month, from circulatory and respiratory collapse after trephining of the skull.

On pathologic examination of the brain multiple laminar softenings were noted throughout the cerebral cortex, most marked in the parietal region of each side. The pial arteries showed calcification of the media; intimal proliferation was present in these vessels and in the large basal arteries.

In the areas of softening there were a marked proliferation of the capillaries and an abundance of phagocytic cells containing fat. About the vessels were accumulations of cells from which gradations could be traced to the fat-laden macrophages. The nature of these cells and the question of the origin of phagocytic cells in the brain, apart from microglia cells, are discussed.

Other reported cases of cortical encephalomalacia in infants are summarized. The condition appears to represent an early stage in the development of diffuse or lobar cerebral sclerosis, a common lesion in cases of infantile cerebral paralysis.

The lesions appear to be due to alterations in the circulation of the cerebral cortex. Actual vascular occlusion is rarely found, and it is believed that vasomotor disturbances may play an important rôle in the pathogenesis of this disease.

CLINICOPATHOLOGIC STUDY OF ALZHEIMER'S DISEASE

RELATIONSHIP TO SENILE CONDITIONS

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Alzheimer's disease is still considered a rare and unusual condition in spite of the fact that about one hundred cases have been reported. Most of the cases occurred in the European clinics, though some of the earliest instances of the disease were described in the American literature. In the period from 1916 to 1928 only one case [1] was recorded in the United States. According to our experience, the disorder is by no means uncommon. Thus, at the Foxborough State Hospital approximately 4 per cent of all the cases in which necropsy was performed proved to be instances of Alzheimer's disease.[2] As this hospital draws from the same general population as do most other state institutions, it probably furnishes a sample which is representative of the whole group. That more cases have not been reported suggests that there is a lack of integration between clinical psychiatry and the basic sciences which have supplied the foundation for many of the important scientific contributions.

One of the more immediate reasons for the frequent lack of recognition of Alzheimer's disease is that there has been a tendency to regard it as a purely histologic entity. The clinical picture is still poorly understood. One usually thinks of the disorder as an atypical form of senile dementia which occurs in comparatively young persons and which can be diagnosed only by microscopic observations. While we do not subscribe to the conception that Alzheimer's disease is merely a variety of

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1. Uyematsu, S.: Pathology of Senile Psychoses: The Differential Diagnostic Significance of Redlich-Fischer's Miliary Plaques, J. Nerv. & Ment. Dis. **57**:1, 1923.

2. During the years from 1926 to 1934 postmortem examinations were performed in two hundred and thirty-four cases, nine of which were found to be instances of Alzheimer's disease.

senile dementia, the fact that it shows histologic changes essentially similar to the lesions present in the latter disease suggests that similar factors may operate in the two conditions. Thus, anything that throws light on the nature and origin of Alzheimer's disease should contribute to knowledge of senile dementia, which in many respects is still obscure. A consideration of senile dementia leads in turn to the problem of its relationship to normal old age. It is evident, then, that in a broad discussion of Alzheimer's disease one must include also the problems of senility in its normal and pathologic aspects.

A study of the relations possibly existing between Alzheimer's disease, senile psychosis and normal old age may take its starting-point from well known observations on the pathologic characteristics of these conditions. In Alzheimer's disease the brain shows as the essential feature widespread cellular changes of a nonspecific nature, a great abundance of senile plaques and many lesions of the neurofibrils of the Alzheimer type. In senile dementia there are fewer plaques, and lesions of the neurofibrils may be entirely absent. If the latter changes occur, they are present in much smaller numbers and are less widely distributed than the fibrillar lesions in Alzheimer's disease. The chief feature of the normal senium is generalized degeneration and atrophy. It was at first thought that plaques occurred only in persons with senile and so-called presenile psychosis, but numerous investigators [3] have pointed out that the lesions may be encountered in persons of advanced age who show no evidence of mental disorder. At this point it is also necessary to remember that plaques and lesions of the neurofibrils may be observed in conditions which have nothing to do with senility. Thus, Schaffer [4] and Lafora [5] noted the presence of fibrillar changes of the Alzheimer type in a case of familial spastic paralysis and in one of schizophrenia. Schnitzler [6] reported a case of myxedema in which many lesions of the

3. (*a*) Simchowicz, T.: Histologische Studien über die senile Demenz, in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1910, vol. 4, p. 267. (*b*) Fischer, O.: Ein weiterer Beitrag zur Klinik und Pathologie der presbyophrenen Demenz, Ztschr. f. d. ges. Neurol. u. Psychiat. **12**:99, 1912. (*c*) Fuller, S. C.: A Study of the Miliary Plaques Found in Brains of the Aged, Am. J. Insanity **68**:147, 1911-1912. (*d*) Grünthal, E.: Klinisch-anatomisch vergleichende Untersuchungen über den Greisenblödsinn, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:763, 1927.

4. Schaffer, K.: Ueber hereditäre spastische Spinalparalyse, Deutsche Ztschr. f. Nervenh. **73**:101, 1922.

5. Lafora, G. R.: Zur Frage des normalen und pathologischen Senium und der Pathologie der Senilität, Ztschr. f. d. ges. Neurol. u. Psychiat. **13**:469, 1912.

6. Schnitzler, J. G.: Zur Abgrenzung der sogenannten Alzheimerschen Krankheit, Ztschr. f. d. ges. Neurol. u. Psychiat. **7**:34, 1911.

neurofibrils were shown but no plaques. Van Bogaert and Bertrand [7] observed both types of alteration in two cases of amyotrophic lateral sclerosis. Lüthy [8] noted plaques in the brain of a patient who presented a clinicopathologic picture typical of multiple sclerosis, and Alzheimer [9] observed the lesions in the brain of a patient who died of tabes dorsalis at the age of 31.

Other instances could be mentioned, but enough have been cited to suggest that the histologic changes occurring in Alzheimer's disease and in senile conditions are not an expression of any one disease process but an indication of a special type of tissue reaction which may occur in response to a variety of exogenous and endogenous agents. Since Alzheimer's disease presents this tissue reaction in its most pronounced form, it seems of interest to devote particular attention to this disorder. It is with this purpose in view that we describe the following cases.

REPORT OF CASES

CASE 1.—Since this case has been reported previously by one of us (J. K.),[10] only a summary will be presented in this paper. A man, aged 49, looked distinctly younger than a person of his age. The illness began at the age of 45, with changes in behavior, sleepiness, intellectual impairment and inability to perform ordinary tasks. There were gradually increasing loss of memory, confusion and deterioration of habits, with the development of muscular hypertonicity and loss of associated movements. Later euphoria, restlessness, perseveration and echolalia were noted. The reactions to serologic tests were negative. The patient had a generalized convulsive seizure two months after his admission to the hospital and died three days later, at the age of 49. Necropsy revealed bronchopneumonia and marked atrophy of the cerebral cortex, which was most pronounced in the frontal lobes. Microscopic examination of the cerebral cortex disclosed widespread cellular changes, considerable loss of cells, many senile plaques and numerous neurofibrillar lesions of the Alzheimer type. The putamen, thalamus and caudate nucleus showed astrocytic proliferation and numerous senile plaques (fig. 1).

In this case certain features were presented which are not usually encountered in Alzheimer's disease. The onset of the illness was characterized by marked drowsiness, and there was generalized muscular rigidity, with loss of associated movements. These features led to a

7. Van Bogaert, L., and Bertrand, I.: Pathologic Changes of Senile Type in Charcot's Disease, Arch. Neurol. & Psychiat. **16**:263 (Sept.) 1926.

8. Lüthy, F.: Ueber einige anatomisch bemerkenswerte Fälle von multipler Sklerose, mit besonderer Berücksichtigung der Grosshirnrinde und des Kleinhirns, Ztschr. f. d. ges. Neurol. u. Psychiat. **130**:219, 1930.

9. Alzheimer, A., quoted by Perusini, G.: Ueber klinisch und histologisch eigenartige Erkrankungen des späteren Lebensalters, in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1909, vol. 3, p. 297.

10. Kasanin, J., and Crank, R. P.: Alzheimer's Disease, Arch. Neurol. & Psychiat. **30**:1180 (Nov.) 1933.

diagnosis of epidemic encephalitis when the patient was first admitted to the psychiatric ward of a general hospital. Physically the patient appeared much younger than a person of his age. Pronounced intellectual deterioration, overactivity, with childish euphoric behavior, and a tendency to perseveration and echolalia occupied the foreground of the clinical picture in the later stages of the illness. Clinically the case resembled certain instances of Pick's disease, and it was, therefore, of interest that macroscopic examination of the brain showed cortical

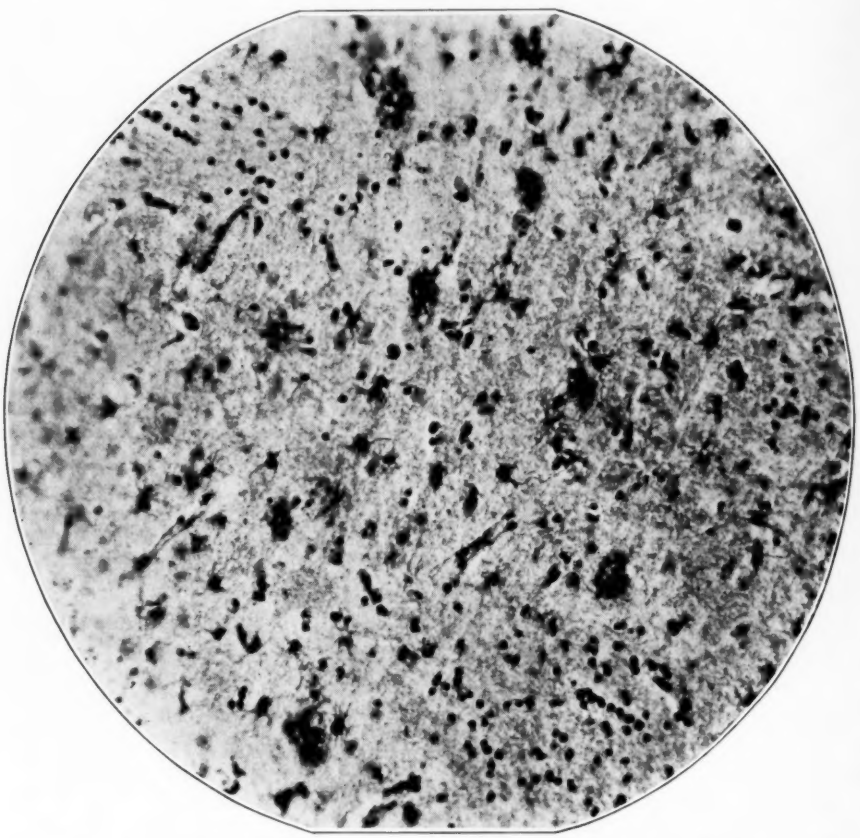

Fig. 1 (case 1).—Section from the caudate nucleus, showing senile plaques and neuroglial proliferation. Penfield modification of the Hortega stain; × 210.

atrophy, which tended to be circumscribed in its distribution. The marked involvement of the basal ganglia may perhaps account for the signs of involvement of the extrapyramidal system observed in this case.

CASE 2.—*Gradual development of confusion and loss of memory at the age of 53; progressive intellectual deterioration until the patient died at the age of 61. Necropsy revealed bronchopneumonia, bronchiectasis, cortical atrophy, many senile plaques and neurofibrillar lesions of the Alzheimer type.*

History.—R. A. W., a man aged 60, was admitted to the State Hospital for Mental Diseases at Howard, R. I., on March 26, 1933. A maternal uncle had suffered from epileptic seizures, which disappeared during middle age. A younger sister was well. As a boy the patient was active and strong, good-natured, pleasant, somewhat shy and easily embarrassed. He had been married, his wife having died fifteen years before. The two children were healthy. One pregnancy had resulted in miscarriage. The patient was a good mixer and was well liked. He was described as practical and a leader. He was fastidious, intelligent and dependable. For twelve years he was an express agent in a railroad station; he also operated a blacksmith shop of his own for five years. After this, he worked as a machinist in a large cotton-manufacturing plant and was so efficient and useful that he was kept for a long time after he became sick. Twelve years before his admission to the hospital the patient received a severe blow on the head, which rendered him unconscious. He remained at home for two weeks. For ten years prior to his admission he had complained of headache, which he described as a bad feeling in the head. He was a moderate drinker. Mental changes were first noted at the age of 53, when it was observed that the patient was becoming confused and forgetful. He continually complained of a "bad feeling" in the head. Memory showed increasing impairment, and he was discharged from work two and a half years before his admission to the institution because he was confused and incompetent to perform even the most simple tasks. Six months later it became obvious that he was not able to care for himself, and a sister took him to live with her. He had to be shown the way to his room at night; he was unable to find the bathroom and was careless in his habits. He did not leave the house during the day but prowled around at night. Occasionally he went out and came back exhausted. He seemed to have frightful dreams and slept little. He often slept with his clothes on, and his overcoat and hat. At times he talked to himself. He was emotionally unstable and cried on slight provocation. He became progressively less active and often stood in one position for hours. When company came he made an effort to enter into the conversation, but this resulted in failure. He began to hide articles. When his father became ill a month before the patient's admission to the hospital, the patient did not seem to appreciate this. He often disturbed his father by entering and leaving the room repeatedly, and suddenly he conceived the idea that his father had died and that his sister had appropriated the articles which should have belonged to him. He claimed various household articles as his own and threatened to "fix" his sister. He became so agitated that the family finally consented to commitment.

Examination.—The patient was well developed but poorly nourished. The heart sounds were poor in strength and quality. There was slight edema of the feet and ankles. The blood pressure was 128 systolic and 86 diastolic. Neurologic examination revealed unsteadiness in gait, with slight tremors of the outstretched hands and swaying on standing with the eyes closed. The vessels of the ocular fundi showed moderate arteriosclerosis. The peripheral arteries were moderately sclerosed. Repeated psychiatric examinations showed that the patient was extremely confused. He did not know where he was and could answer only the most simple questions. Memory was so poor that he could give no information about himself except a few isolated facts. He could not tell whether his wife was living, and when he was asked his age he gave it as "50 or something." He remembered that he had operated an express business and forgot that he had been a machinist. The mood was one of apathy, but occasionally he showed faint resentment because he was unable to recall events and names. He

complained of being nervous, without being able to state the symptoms. In regard to the idea that his father was dead and his sister had taken away his property his reaction was variable. Thus, at one time he thought that his father was living and at another that he was dead. He was observed to lie motionless for hours. His attitude was one of marked indifference and apathy, with occasional desperate attempts to become more active and interested in things. At a staff conference Dr. A. P. Noyes made a diagnosis of Alzheimer's disease.

Laboratory Observations.—Examinations of the urine and blood gave negative results. The Wassermann reaction of the blood and that of the spinal fluid were negative. The spinal fluid contained 1 cell, and the reactions to the colloidal gold and mastic tests were normal. A roentgenogram of the skull showed nothing abnormal.

Course of the Illness.—Edema of the legs, with redness, developed. This condition improved with rest and elevation of the feet. The patient led a purely vegetative existence for about a year, becoming more and more confused and disinterested. He wandered around the ward for hours at a time without any special purpose. He lost much weight and grew gradually weaker. On Jan. 5, 1934, he became cyanotic and was put to bed. He did not get up after this; he became progressively weaker, and there was increasing edema of the ankles. On July 13, 1934, diarrhea developed, and the patient died.

Gross Observations at Necropsy.—Necropsy was performed one hour after death (by Dr. R. P. Crank). The skin was dry and inelastic over the trunk, head and upper extremities. There was moderate edema of the feet and legs. Both lungs showed diffuse bronchiectasis, with purulent material. There were scattered areas of bronchopneumonia in the lower lobes. Both lungs were diffusely edematous and heavy. The myocardium was somewhat pale and friable and contained an excess of fibrous tissue. The aorta showed slight sclerotic changes. There was moderate diffuse thickening of the coronary and peripheral arteries, without evidence of narrowing of the lumens. There were hyperplasia of many mesenteric lymph nodes and central necrosis with caseation in a few. The leptomeninges were slightly opaque. The cerebral blood vessels appeared slightly thickened. The cerebral hemispheres showed generalized atrophy, which was less advanced in the regions adjacent to the central fissure than elsewhere. The lateral ventricles were somewhat dilated.

Microscopic Examination.—All parts of the cerebral cortex showed moderate diminution in the number of nerve cells, without noteworthy disturbances of the architecture. In sections stained with silver salts numerous senile plaques and neurofibrillar lesions of the Alzheimer type were observed. These alterations were present in all parts of the cerebral cortex but were less abundant in the precentral and the postcentral gyrus than in other parts of the brain.

The chief feature in this case was gradually increasing intellectual impairment, leading within a few years to profound mental deterioration. In contrast to the condition in case 1, the patient presented some of the somatic changes that one usually associates with senile conditions. The emotional instability suggested cerebral arteriosclerosis, but, owing to the steady progression of the symptoms and the profound dementia, a diagnosis of Alzheimer's disease was made. The case may be considered to be a typical instance of the disease.

CASE 3.—*A man became sexually impotent at the age of 57 and blamed his wife for being overdemanding sexually. Three years later there were impairment of memory and gradually increasing intellectual deterioration. The patient died at the age of 66. Necropsy revealed changes typical of Alzheimer's disease in all parts of the cerebral cortex, with a considerable number of plaques in the putamen, caudate nucleus and thalamus.*

History.—H. B. M., a white man aged 63, was admitted to the Foxborough State Hospital on Dec. 22, 1930. The maternal grandfather was said to have been "peculiar." The father was a heavy drinker; he died when the patient was 9 years old. There were five siblings, one of whom died in childhood. One brother, a heavy drinker, was accidentally killed fifteen years before. The various members of the family were considered "sensitive." The patient had had little schooling, reaching only the fourth grade. Apparently he had difficulty in doing the school work, but he was always able to support himself and his family. He worked as a teamster and later as a janitor of a large book-bindery. The patient was described as retiring and timid, lacking in initiative and good-natured but not affectionate. He was married and had two children. One son was suffering from schizophrenia and had been a patient in the Foxborough State Hospital since June 1932. Six years before his admission to the hospital, the patient became impotent sexually. He was irritable and worried about his impotence and accused his wife of demanding too much of him sexually. Approximately three years later he began to show impairment of memory. On several occasions he became lost on attempting to visit friends. He was jealous of his wife, accusing her of having men in the house. He grew more and more inefficient in work and was discharged in May 1929. He had outbursts of temper, at times threatening violence to his wife. He often sat in a dark corner of the room without moving for hours. He began to have difficulty in naming familiar objects and in doing ordinary tasks, such as dressing and looking after the furnace fire. He became untidy in habits, sometimes leaving soiled toilet-paper in the dining room.

Examination.—The patient was poorly developed and poorly nourished. The hair was gray and scanty. There was bilateral arcus senilis. The skin was dry and scaly. There was an inguinal hernia on the left side. The blood pressure was 120 systolic and 70 diastolic. The right lower extremity showed varicose veins. The pupils reacted sluggishly to light, but their reaction was more active in accommodation. There were slight tremors of the tongue and fingers. The tendon reflexes were very active. The gait was of wide base, and there was a slight Romberg sign. The patient was quiet and pleasant and appeared mildly euphoric. There was deterioration, and memory was extremely defective. He seldom spoke spontaneously but answered questions readily. At times he seemed to have difficulty in comprehending remarks made to him. His responses were relevant, but he occasionally used peculiar expressions or words. Thus, when he was asked to name the month, he replied: "Well, it is pretty hard for me to place it. I have been getting along good until today. I can't get them pulled together very well today, but I have been doing well for quite a long time." When he was requested to give the year, he answered: "It isn't far from Christmas. We had Christmas not very long ago. That's one thing I got lodged up a little." He named most objects correctly. When he was unable to do so, he could indicate their use. He was unable to perform even simple calculations. He made frequent mistakes in naming colors. There was no definite evidence of apraxia. He wrote his name illegibly. Several letters could not be deciphered, and one was repeated. He recognized objects in pictures but did not grasp the significance of the picture as a whole.

Laboratory Observations.—The blood contained 5,000,000 red cells and 6,000 white cells per cubic millimeter, with 80 per cent hemoglobin, and 81 mg. of sugar and 587 mg. of chlorides per hundred cubic centimeters. The Wassermann reaction of the blood and that of the spinal fluid were negative. Examination of the urine showed nothing abnormal. The ratio of distribution of bromide between the blood and the cerebrospinal fluid was 3. The calcium content of the spinal fluid was low, being 4.2 mg. per hundred cubic centimeters, as compared with 9.5 mg. for the blood.

Course of the Illness.—The patient remained in an underactive condition for several months. There was gradually increasing confusion. He became restless and wandered aimlessly about the ward. He was untidy in habits. He grew gradually weaker and in January 1933 became completely bedridden. Signs of congestion of the lungs developed, and he died on April 2, 1933.

Gross Observations at Necropsy.—The aorta and coronary arteries showed slight arteriosclerosis. The lower lobes of both lungs were congested. The liver presented a nutmeg appearance. The upper part of the jejunum showed several small diverticula. The brain weighed 1,060 Gm. The pia-arachnoid was slightly opaque. There was a small recent hemorrhage in the subarachnoid space in the region of the left temporal pole. The cortical convolutions were atrophied, this being most marked in the frontal lobes. The lateral ventricles were moderately dilated. The basal vessels were delicate.

Microscopic Examination.—All parts of the cerebral cortex showed loss of cells, senile plaques and neurofibrillar lesions of the Alzheimer type. Hyaline-like alterations were common in the small vessels of the pia and choroid plexus. Typical hyaline changes were occasionally encountered. The severest cellular changes were observed in the parietal and temporal lobes, though the alterations were also pronounced in the anterior part of the frontal region. In these areas there was frequently considerable disorganization of the cortical architecture, with the upper half of the cortex presenting severer damage than the lower. The largest number of plaques, 102 per low power field on an average,[11] occurred in the hippocampal gyrus (fig. 2). Almost as many were observed in the parietal and temporal regions and the anterior portion of the frontal region. The occipital lobe showed the smallest number, 43 per low power field. The lesions of the neurofibrils were most abundant in the pyramidal band of the cornu ammonis, the majority of the nerve cells being involved. Apart from this, the lesions occurred with greatest frequency in the areas presenting the largest number of plaques, though they were less evenly distributed than the plaques. Lesions of the neurofibrils were uncommon in the occipital lobe and the precentral gyrus. The putamen and the caudate nucleus showed a moderate number of plaques (up to 25 per low power field), with considerable neuroglial proliferation. Plaques were abundant in the thalamus, 40 being counted in many low power fields. A few were observed in the central gray matter about the third ventricle.

This case illustrates the fact that in certain instances Alzheimer's disease may show features which suggest a close relationship to senility. The onset of the illness with sexual impotence, and the senile changes in the skin and eyes, pointed distinctly to senile involution. The clinical picture was characterized by profound intellectual deterioration, which

11. The plaques were counted in this case and in the following cases with a Zeiss binocular microscope, objective 8, numerical aperture 0.2, ocular × 10.

occurred at an age earlier than that ordinarily regarded as the senile period. In such cases the chief difference between Alzheimer's disease and senile dementia is quantitative, the changes being severer in the former disease than in the latter. It should be emphasized, however, that some patients with Alzheimer's disease present none of the usual somatic manifestations of senility. This was illustrated in case 1. Another striking example was the case reported by Lowenberg and one of us (D. R.),[12] in which the patient gave birth to a healthy child several years after the outbreak of the mental illness.

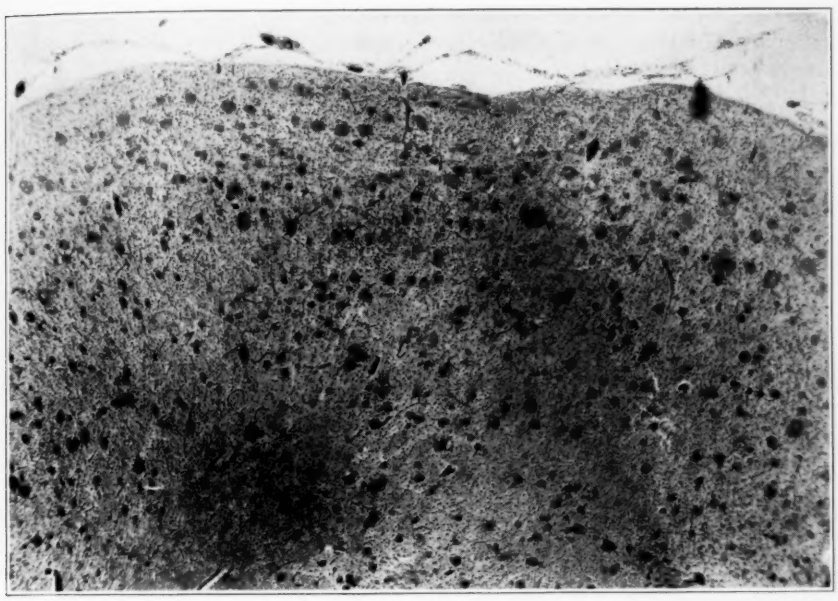

Fig. 2 (case 3).—Section from the hippocampal gyrus, illustrating the large number of senile plaques that occur in cases of severe Alzheimer's disease. Dieterle-Neumann modification of the Hortega stain; × 33.

CASE 4.—*A woman, aged 52, became infatuated with a young man; there followed an erotic state, with wish-fulfilling fantasy and behavior and later confusion.. At 56 there were marked impairment of memory, confusion, rambling and disconnected speech and mild elation, with delusions and hallucinations. There was only slight evidence of progressive intellectual deterioration during the following years. The patient died at the age of 69. Necropsy disclosed bronchiectasis, bronchopneumonia, arteriosclerosis, atrophy of the brain with cellular changes, many senile plaques and lesions of the neurofibrils in all parts of the cerebral cortex and considerable involvement of the basal ganglia.*

12. Lowenberg, K., and Rothschild, D.: Alzheimer's Disease: Its Occurrence on the Basis of a Variety of Etiologic Factors, Am. J. Psychiat. **11**:269, 1931.

History.—M. C., a white woman aged 56, was admitted to the Foxborough State Hospital on June 7, 1918. The family history was of no significance. The patient was sickly during childhood and was unable to attend school regularly because of poor health. She was said to have been a bright student and active and cheerful. She remained at home, keeping house for her parents and later for a brother. She was described as prudent and a good housekeeper. She had shown practically no interest in the opposite sex until four years before, when she became infatuated with a young man who lived near-by. About a year later she became restless and thought that this man cared for her. She dyed her hair, became more and more restless and expressed the belief that persons were talking about her. She became suspicious of her brother. She began to frequent moving picture theaters. She was confused on some occasions. The mood varied; at times she wept and at times sang. Although her appetite was ravenous, she lost weight steadily. She became untidy and refused to change her clothing. She became so nosiy and troublesome that she was sent to the Danvers State Hospital on March 1, 1916. There she was disoriented and confused. Memory was very defective. She had hallucinations and delusions. She said she had been poisoned and claimed that she was owner of the building. Occasionally she held conversations with imaginary persons in her room. She was irritable and profane. Later she became more agreeable and frequently laughed in a silly manner. Her conversation was described as incoherent. She was transferred to the Foxborough State Hospital on June 7, 1918.

Examination.—The patient was poorly developed and poorly nourished. There was slight arcus senilis. The breath sounds were harsh in the apical regions. The radial arteries were sclerosed and tortuous. The blood pressure was 150 systolic and 95 diastolic. Neurologic examination gave essentially negative results. The patient presented a disheveled appearance. She was elated and friendly. She expressed fantastic delusions, some of which were changeable. She believed that she was a man and that the hospital was a house of ill repute. She stated that when an aunt died her enemies burned her in a stove and burned her little sister's hand to make her appear guilty. She thought that the other patients were her old friends. She spoke of hearing her father and uncle talking to her night and day, their voices being in the walls. Her speech was described as rambling and disconnected. She was completely disoriented. Memory was very defective, and she showed a marked tendency to confabulate. Judgment was poor, and there was no insight. A diagnosis of senium praecox was made on Aug. 28, 1918.

Laboratory Observations.—Examination of the urine showed nothing abnormal. The Wassermann reaction of the blood was negative. The blood contained 5,270,000 red cells and 9,800 white cells per cubic millimeter and 85 per cent hemoglobin.

Course of the Illness.—There was no essential change in the mental condition of the patient during the four years after her admission to the hospital. She was unstable emotionally, at times becoming irritable and aggressive. She often appeared to react to auditory hallucinations. She misidentified persons and thought that most of the other patients were masquerading and intended to injure her. She was able to do work in the sewing room until 1925, though she gradually became less efficient. Occasionally there was a slight increase in temperature, with considerable cough. On Feb. 7, 1925, it was noted that her remarks were becoming more incoherent. "If a person killing now, we ought to kill any more; I never kill, tried to save them and threw them into the weather." In January 1926, examination of the lungs disclosed defective expansion of the upper lobe

of the right lung and diminished resonance in the right apex, with moist crepitant râles. During the following years the patient spent most of the time in bed, owing to general weakness, chronic cough and frequent increase in temperature. Examination on June 22, 1927, disclosed considerable emaciation, moderate generalized muscular hypertonicity, exaggerated tendon reflexes, a questionable Babinski sign on the left and a Rossolimo sign bilaterally. The patient was mildly euphoric but rather inactive. When asked how old she was she answered: "I don't know; I couldn't tell you to save my soul. I am not very old or very young. I have six children all told. My dear little Muffie, the dear little soul. I wanted to know off my name altogether, but Mr. Harding, he was my, he used to always attend me. I went with him for three or four years. Said he had one or two sons. No, I have never had any inclination of going with men." Here the patient pointed to the lower part of her abdomen and said that Mr. Harding had "made a boy and a girl inside of me." She was disoriented, and her memory seemed defective. She showed a marked tendency to confabulate. When she was asked whether she was then in a hospital, she replied: "Yes, I forgot myself. My sister when she'd sit down she would say there's a string going up now. It's nice, but I go right up and fly with the fellows. Young fellows get flies here and get money for it, flying." She also said that Mr. Harding made her "a teacher of the Catholic firm." There was no essential change in the mental condition of the patient during the rest of her stay in the hospital. She grew gradually weaker and became dull and semistuporous. She died on Nov. 3, 1931.

Gross Observations at Necropsy.—There were several decubital ulcers in the region of the sacrum and hips. The heart muscle showed an increase in the amount of fibrous tissue. The coronary arteries and aorta presented marked arteriosclerosis. The left pleural cavity contained a considerable amount of clear yellow fluid. The lungs showed bronchopneumonia. The right lung was adherent and shrunken, and there were numerous dilated bronchi in the lower lobe. The kidneys were small and granular. The liver was congested. The brain weighed 1,000 Gm. There was moderate generalized atrophy of the cortical convolutions. The basal vessels showed numerous yellowish, thickened patches.

Microscopic Examination.—The pia-arachnoid was thickened and fibrotic. With the Nissl stain a diffuse loss of nerve cells appeared in most parts of the cerebral cortex. The parietal and temporal lobes, the anterior part of the frontal region and the cornu ammonis showed the most pronounced alterations. In these areas there was considerable disturbance of the cyto-architecture. Many of the nerve cells were pale and shrunken. As a rule, the changes were greatest in the upper half of the cortex, particularly in the third layer. Marked variations were frequently noted, even in closely adjacent sections. The mildest involvement occurred in the precentral gyrus and the occipital lobe, which were in most places fairly well preserved. There was considerable astrocytic and microglial proliferation, especially in the areas presenting the severest cellular damage. Some of the small vessels of the pia, choroid plexus and white matter showed hyaline-like changes. A few cortical vessels exhibited slight endothelial proliferation with adventitial thickening. The large nerve cells of the putamen and caudate nucleus were pale, and many were shrunken. The nerve cells of the thalamus contained large lipoid accumulations. The Bielschowsky stain and the Dieterle-Neumann modification of the Hortega method revealed many senile plaques in all parts of the cerebral cortex. In the parietal lobe, in which the greatest number were shown, 85 plaques were counted per low power field. They were almost as abundant in the hippocampal gyrus, cornu ammonis and temporal lobe. The precentral gyrus

presented the smallest number, 15 being counted per low power field. The plaques occurred in all the layers of the cortex but were generally most abundant in the third lamina. The putamen, caudate nucleus and thalamus showed a moderate number. A few were observed in the corpus Luysi and the gray matter about the third ventricle. Many neurofibrillar lesions of the Alzheimer type were also observed in the cerebral cortex. They were most abundant in the pyramidal band of the cornu ammonis. In this region most of the nerve cells were involved. In the other portions of the cortex the lesions of the neurofibrils usually occurred with greatest frequency in the areas presenting the largest number of plaques, but they were less evenly distributed than the plaques.

The clinical picture was characterized by certain symptoms similar to those of schizophrenia and by others suggesting organic involvement. The question may, therefore, be raised whether this case was really one of schizophrenia, with the later addition of senile changes. It was evident, however, that organic features, such as confusion and pronounced impairment of memory, were prominent at the beginning and throughout the course of the illness. In fact, these dominated the clinical picture to such an extent that a diagnosis of senium praecox was made in 1918. Doubts were expressed later as to the correctness of this diagnosis, owing to the long duration of the illness and the lack of distinct progression of the symptoms. However, it is now known, as a result of the observations of Malamud and Lowenberg [13] and one of us (D. R.),[14] that the disease may come to a standstill for many years and that even remissions may occur. The patient presented a disturbance of speech which resembled the defect occurring in certain cases of schizophrenia. One of us [14] has pointed out that the disorder of speech in Alzheimer's disease does not conform to the difficulty occurring in the classic types of aphasia but is characterized by general disturbances which indicate a lowering of function to a more primitive level. This is not necessarily inconsistent with the changes in the present case, for Schilder [15] has shown that disturbances of speech associated with organic disease and those associated with schizophrenia are in many respects similar. It may be added that in case 3 reported in a previous communication [14] the patient exhibited a disorder of speech which was in some respects reminiscent of that observed in schizophrenia.

CASE 5.—*A woman at the age of 40 became depressed after the death of several relatives. There followed confusion and progressive intellectual impairment*

13. Malamud, W., and Lowenberg, K.: Alzheimer's Disease: A Contribution to Its Etiology and Classification, Arch. Neurol. & Psychiat. **21**:805 (April) 1929.

14. Rothschild, D.: Alzheimer's Disease: A Clinicopathologic Study of Five Cases, Am. J. Psychiat. **91**:485, 1934.

15. Schilder, P.: Brain and Personality, Nervous and Mental Disease Monograph 53, Washington, D. C., Nervous and Mental Disease Publishing Company, 1931.

and later restlessness, incoherence, perseveration, apraxia and disturbance of spatial orientation. She died at the age of 62. Necropsy revealed: carcinoma of the ovary, with metastases to the mesentery and liver; peritonitis; cortical atrophy of a circumscribed nature, with cellular changes, many plaques and lesions of the neurofibrils in all parts of the cerebral cortex, and moderate involvement of the basal ganglia.

History.—M. G. J., a white woman aged 61, was admitted to the Foxborough State Hospital on March 10, 1933. The parents were said to have "died of old age." There were eight siblings, two of whom died of a "shock" in later life. One sister was suffering from schizophrenia at the time the patient was admitted to the hospital and had been in a hospital for the treatment of mental diseases since 1905. The patient was married and had had three children, one of whom died in infancy. The others were well. The husband was healthy. The patient was described as active, good-natured, a good mixer, though somewhat sensitive, and a hard worker. She had begun to show mental changes during the menopause, twenty years before. Several deaths had occurred in the family about this time. She began to worry and had spells of crying. She expressed the idea that she was "dirty." The crying spells ceased within a few months, but memory became defective. At times she was confused. She sometimes put tea in the kettle instead of in the teapot, and if told to pick up something frequently took the wrong object. She often walked back and forth, wringing her hands or fumbling with her clothing. She sometimes stood in front of the mirror for hours, talking to herself. Speech became rambling and disconnected. These symptoms gradually increased. About two years before her admission to the hospital, she became restless at night. She was unable to find her way about the house and could not use eating utensils. Memory showed marked impairment, especially for recent events. At times she carried on conversations with imaginary persons. She was unable to recognize any one. Finally, she became so restless and difficult to care for that she was committed to the hospital.

Examination.—The patient was well developed and well nourished. There was edema of both feet. The lower extremities showed varicose veins. The blood pressure was 158 systolic and 84 diastolic. There were fine tremors of the outstretched fingers. The patient was restless and confused. She wandered about the ward constantly, talking to imaginary persons. She had to be dressed and undressed, and it was necessary to feed her with a spoon. She was untidy in habits and completely disoriented, and memory was markedly impaired. Speech was incoherent, and her replies to questions were often irrelevant. There was a tendency to perseveration. When asked to give her name she answered: "We were on the . . . I can't tell now what the name was." In regard to her age she replied: "I am 12 years old; I guess I am 12 years old, 12 years old." When asked how long she had been in the hospital, she replied, "Why, I have been here, well, I can't remember that many. I wanted to do." To the question "What is this place?" she replied: "Well, just the same as here." When asked what day it was she said: "I should think twenty of a place; Frank would have it." She displayed apraxia and obeyed only a few very simple commands. She was unable to find her way around the ward, though there was no gross impairment of visual acuity. When she was handed an object, she reached out in another direction for it.

Laboratory Observations.—The urine contained a faint trace of albumin and many leukocytes. The Wassermann reaction of the blood and that of the spinal

fluid were negative. Examination of the blood showed 4,370,000 red cells and 11,650 white cells per cubic millimeter, hemoglobin concentration 85 per cent; sugar 88 mg., nonprotein nitrogen 21 mg., calcium 9.2 mg. and phosphorus 3.9 mg. per hundred cubic centimeters. Examination of the spinal fluid revealed no cells. The colloidal gold curve was 0000000000. The spinal fluid contained total protein 25 mg., sugar 63 mg., calcium 4.5 mg. and phosphorus 1.8 mg. per hundred cubic centimeters. The ratio of distribution of bromide between the blood and the spinal fluid was 2.46.

Course of Illness.—There was no essential change in the mental condition of the patient. She grew gradually weaker, however. On Sept. 18, 1933, there were diarrhea and a slight elevation of temperature. She failed rapidly and died on Sept. 22, 1933.

Gross Observations at Necropsy.—Carcinoma of the left ovary, with metastases to the mesentery and liver, was observed. The omentum was adherent to coils of the small intestine, which were bound by recent adhesions. There was generalized peritonitis. The aorta showed a few calcified atheromatous plaques. The brain weighed 1,110 Gm. There was marked cerebral atrophy, which was sharply limited to the frontal lobe anterior to the precentral gyrus, the temporal lobe and the parietal lobe posterior to the postcentral convolution. The atrophy was more pronounced in the left cerebral hemisphere than in the right, with the left frontal lobe presenting the greatest shrinkage. The lateral ventricles were slightly dilated. The basal vessels were not thickened.

Microscopic Examination.—There were severe loss of cells, many senile plaques and an abundance of neurofibrillar lesions of the Alzheimer type in most parts of the cerebral cortex. The left frontal lobe showed the largest number of plaques, with an average of 117 per low power field (fig. 3), as compared with 43 in the right frontal lobe. The average number in the right temporal lobe was 106; in the right parietal lobe, 91; in the right cornu ammonis, 20, and in the right occipital lobe, 27. The neurofibrillar alterations were abundant in all the sections of the cerebral cortex and were more uniformly distributed than the plaques, the occipital lobe presenting almost as many lesions as other parts of the cerebrum. With the Nissl stain the parietal lobe showed the greatest changes. There were marked loss of cells, extensive disturbances of the architecture and pronounced astrocytic and microglial proliferation. With this stain the damage was observed to be almost as severe in the temporal lobe but appeared less marked in the frontal region. The precentral and postcentral convolutions and the occipital lobe presented mild alterations only. The involvement usually predominated in the second and the third cortical layer. Nissl's chronic cellular disease was encountered with greater frequency than were other types of cellular lesions. The vessels of the cortex showed considerable endothelial swelling and proliferation, with adventitial thickening. Hyaline-like vascular lesions were observed but were not common. The choroid plexus exhibited a moderate degree of fibrosis in some places, and hyaline-like changes had occurred in a few of the vessels. A small number of senile plaques were observed in the putamen, caudate nucleus and substantia nigra. In the corpus Luysi plaques were more abundant, and neurofibrillar lesions of the Alzheimer type were occasionally observed. Some of the vessels of the putamen and caudate nucleus were calcified.

In this case a number of interesting features were presented. The onset of the illness in connection with emotional problems should be

noted. Herz and Füngeld [16] have described cases in which affective symptoms were prominent at the beginning of the disorder. In this instance the illness ran a protracted course, but it is becoming more and more evident that psychosis of fifteen or twenty years' duration is by no means rare in cases of Alzheimer's disease. The clinical picture on the patient's admission to the hospital was typical of an advanced stage

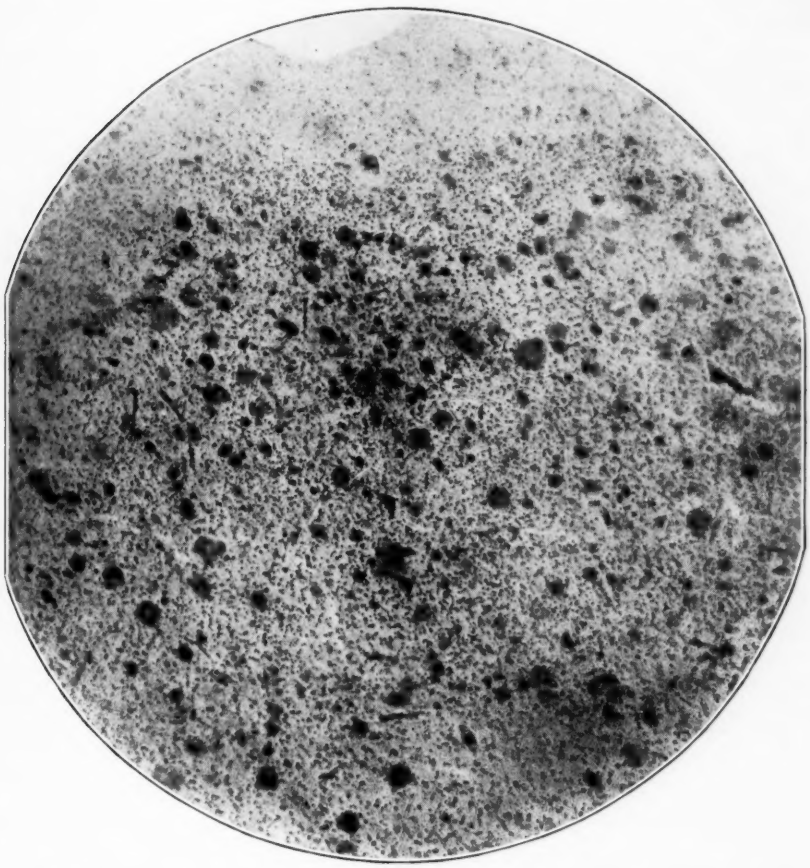

Fig. 3 (case 5).—Section from the left frontal pole, showing great abundance of senile plaques. Dieterle-Neumann modification of the Hortega stain; × 45.

of Alzheimer's disease. Apraxia and high grade disturbances of spatial orientation were observed. The former symptom is not uncommon, but the latter disturbance has not, to our knowledge, previously been described in this disorder. The histologic changes were severer than

16. Herz, E., and Fünfgeld, E.: Zur Klinik und Pathologie der Alzheimerschen Krankheit, Arch. f. Psychiat. **84**:633, 1928.

the lesions observed in most cases and were less evenly distributed than usual. As observed in case 1, there was a distinct tendency toward lobar distribution of the atrophy.

Comment.—In the group of five cases which we have described, slowly progressive psychosis occurred in middle-aged persons. The main feature of the clinical picture was the progressive intellectual impairment, although in the early stages of the illness personal psychologic factors were significant. The illness began rather insidiously and often dated from a personal event in the life of the patient. These factors are illustrated in cases 3, 4 and 5. Chronic somatic disorder was common later in the disease, but there was no evidence of any toxic, infectious or traumatic factor in relation to the onset of the psychosis. In cases 1 and 2 the onset was insidious, and the course of the illness was characterized chiefly by gradually increasing reduction in ability to deal with every-day problems requiring ordinary intelligence and judgment. These are instances of the so-called classic form of Alzheimer's disease.

It is difficult to interpret the emotional factors observed in these cases except from a speculative standpoint. One might use the familiar conception that organic disease releases hitherto concealed trends. The influence which intense emotions may have on the central nervous system still is not known. It is possible that the emotional changes may be a form of compensation or a reaction to the problems of middle age, with the gradual failure of efficiency which often occurs during that period. This point of view will be developed in a future communication.

Since Alzheimer's disease has frequently been looked on as closely allied to senile psychosis, it is worth while to discuss our material from the standpoint of this relationship. It has been emphasized in the past that patients with Alzheimer's disease look prematurely old, but this is not invariably true. In case 1, for instance, the patient actually looked younger than a person of his age; the muscles were firm and well developed, and his skin was devoid of wrinkles. Most observers of the condition have pointed out that from a clinical standpoint Alzheimer's disease differs considerably from senile dementia. In Alzheimer's disease the onset is much earlier than in senile dementia; the course of the illness is more variable, and there are greater intellectual deterioration and more pronounced motor unrest. Patients with Alzheimer's disease frequently display periods of marked apprehension, and there is usually disorder of speech which resembles, but does not completely conform to, the disturbances in classic types of aphasia. There may be focal symptoms of an impure nature, such as the spatial disorientation and apraxia shown in case 5. Occasionally signs of involvement of the

pyramidal tract may be noted, as in case 4.[17] These features differentiate sharply Alzheimer's disease from senile dementia.

The pathologic changes in the cerebral cortex are too well known to require comment. They have been described in detail by one of us [14] in a previous communication. However, it is not yet widely recognized that the basal ganglia are frequently involved in Alzheimer's disease. In four of the cases in this series, damage of the putamen and caudate nucleus was shown, and changes in the region of the substantia nigra were not uncommon. Clinically there may be few indications of these alterations, though a slight increase in muscular tonus of the type described in the German literature as senile muscular rigidity is often observed. That a parkinsonian syndrome may occur was shown by case 1. This case is, to our knowledge, the only instance of Alzheimer's disease in which such a picture has been reported. It was of interest that even in this case the pallidum presented little evidence of involvement, which confirms the old observation that the pallidum is relatively invulnerable to the process in Alzheimer's disease. Herz and Fünfgeld [16] attributed the motor unrest, which is a prominent feature in many cases, to damage of the caudate nucleus. While it is true that the caudate nucleus is often affected, certain other basal ganglia, especially the putamen, are altered with equal frequency and severity. In view of the widespread distribution of the changes, it seems difficult to make exact clinicopathologic correlations with any degree of certainty. In this connection it may be noted that the thalamus was definitely involved in cases 1, 3 and 4, and yet the patients failed to show any of the well known clinical features of a thalamic syndrome.

In certain cases Alzheimer's disease may strongly resemble Pick's lobar atrophy. Case 1 was originally regarded as an instance of Pick's disease, for the clinical picture seemed consistent with the usual description of this disease. Even macroscopic examination of the brain lent support to this diagnosis, the cortical atrophy predominating greatly in the frontal lobes. Microscopic examination alone established the diagnosis of Alzheimer's disease. The brain in case 5 also showed circumscribed atrophy, and the microscopic changes were less evenly distributed than is usual in Alzheimer's disease. These two cases suggest the possibility that there are transitional states between Alzheimer's disease and Pick's lobar atrophy.

It is evident from these observations that the clinical picture in Alzheimer's disease may vary considerably in different cases. Never-

17. Definite hemiparesis, with increased reflexes and a Babinski sign, has been observed in a case which came to our attention too recently to be included in the present paper. The histologic picture was typical of that in a severe form of Alzheimer's disease.

theless, we do not agree with Critchley's [18] statement that it is not possible to diagnose Alzheimer's disease during life. In our experience, the diagnosis can be made with a fair degree of certainty in the majority of instances if one remembers that the core of the clinical picture is formed by a definite "organic syndrome," with the special features and modifications that have already been described. In three of the instances in our series (cases 2, 3 and 5) the diagnosis was made correctly on clinical grounds, and in a fourth instance (case 4) the presence of Alzheimer's disease was strongly suspected. The differences between Alzheimer's disease and senile dementia have already been mentioned. It may be difficult or impossible to distinguish between Pick's lobar atrophy and Alzheimer's disease in certain instances (as in case 1), though the former disease is, in our opinion, rare as compared with the latter disorder. Occasionally the clinical picture may resemble that observed with cerebral arteriosclerosis or even with tumor of the brain. It is therefore apparent that histologic investigation is of great importance in establishing the diagnosis. At the same time, we wish to emphasize the less recognized fact that the pathologic changes, taken in themselves, are not an infallible indication that one is dealing with genuine Alzheimer's disease. They may occur in conditions which obviously do not belong clinically to the Alzheimer group. This point is illustrated by the following two cases:

CASE 6.—*A man, aged 57, had ulcers of a leg. Several weeks later he became confused, stuporous and delirious. He presented restlessness, mild euphoria, confusion, marked impairment of memory and a tendency to confabulation. Gangrene of the foot developed, and the patient died ten days after admission to the hospital. Necropsy revealed gangrene of the foot, with infection spreading up the leg, congestion of the lungs, arteriosclerosis and toxic changes in the visceral organs. The brain showed widespread cellular changes, senile plaques and neurofibrillar lesions of the Alzheimer type, with vascular changes in the choroid plexus.*

History.—W. F. W., a white man, was admitted to the Foxborough State Hospital on Sept. 25, 1933. The family history was of no significance. The patient was married but had been divorced many years before. There was one daughter, who was well. The patient had been a heavy but inconstant drinker. He had been temperate in the use of alcohol during the past three years. He was described as active, talkative and "nervous and jumpy." He mixed well with people and had been proficient in sports. He had tried his hand at many occupations and was regarded as a roamer. During the past three years he had been working as a chef in a small hotel. Two months before his admission to the hospital he consulted a physician for treatment for ulcer of the leg. The condition was regarded as a varicose ulcer. The patient was seen by this physician on several occasions, but no mental abnormality was noted. He complained of considerable pain in the leg and difficulty in walking. A few weeks later he became sleepless and restless. At times he seemed to be in a stupor and at other times confused. He began to "talk deliriously" and finally became so restless that it was impossible to care for him at home.

18. Critchley, M.: Discussion of the Mental and Physical Symptoms of the Presenile Dementias, Proc. Roy. Soc. Med. **26**:1077, 1933.

Examination.—The patient was poorly developed and poorly nourished. The lower extremities showed varicosities and numerous brownish areas on the anterior aspects of the legs which suggested healed ulcers. There were two large ulcers on the left foot, one on the dorsum and the other immediately anterior to the external malleolus. The borders of these ulcers were irregular. The left foot was cyanotic and slightly swollen. The blood pressure was 150 systolic and 90 diastolic. The radial arteries were thickened. There were tremors of the fingers. Apart from this, neurologic examination disclosed nothing abnormal. The patient was restless at times but usually remained quietly in bed. As a rule speech was coherent and relevant, though longer utterances tended to become somewhat irrelevant. He was mildly euphoric and disoriented as to time and place. Memory was markedly impaired, particularly for recent events. He showed a tendency to confabulate. He exhibited poor judgment, and insight was completely lacking.

Laboratory Observations.—The urine contained a faint trace of albumin and a few granular casts. The Wassermann reaction of the blood was negative. Examination of the blood revealed 4,330,000 red cells and 23,100 white cells per cubic millimeter, hemoglobin concentration 77 per cent, sugar 82 mg., nonprotein nitrogen 27 mg., chlorides 593 mg. and calcium 10.4 mg. per hundred cubic centimeters.

Course of the Illness.—There was no essential change in the mental condition of the patient. The foot became definitely gangrenous, and the lymph nodes in the inguinal region on the left, swollen and reddened. The rectal temperature ranged around 100 F. during the first six days after the patient's admission to the hospital. On the seventh day it was 102 F., and on the eighth, 104 F. During the last two days of the illness it ranged around 106 F. The patient grew rapidly weaker, and the pulse became rapid and thready. He died on Oct. 5, 1933.

Gross Observations at Necropsy.—Necropsy was performed twenty-one hours after death. The left foot was bluish black, and there were several ulcerations on the dorsum of the foot and one in the region of the external malleolus. The left leg was swollen to the level of the knee, and the lymph glands in the inguinal region on the left were enlarged. The lower lobes of the lungs were congested. The heart muscle was flabby. There was marked sclerosis of the coronary arteries. The abdominal aorta showed a few calcified plaques. The spleen was congested. There was cloudy swelling of the liver and kidneys. The brain weighed 1,260 Gm. There were several small fresh blood clots between the dura and the arachnoid in the middle fossa of the skull on the left. The basal vessels showed a few yellowish thickened areas.

Microscopic Examination.—Staining of the cerebral cortex with thionin disclosed a paucity of nerve cells, which was somewhat spotty. The loss of cells was extensive in Sommer's sector of the cornu ammonis. In other parts of the brain only a slight decrease was observed. The third layer was chiefly affected. Many of the nerve cells were pale, the Nissl bodies appearing as fine, dustlike material. As a rule, the cortical architecture was not seriously disturbed. There was moderate astrocytic and microglial proliferation. The temporal and parietal lobes presented the severest alterations. The occipital lobes were fairly well preserved. The cortical vessels exhibited moderate endothelial swelling and adventitial proliferation. There was an increase in the amount of connective tissue in the choroid plexus, and many of the vessels showed hyaline-like changes. Similar lesions were observed in some of the pial and cortical vessels. A few of the larger arteries showed mild arteriosclerosis. Calcium deposits were occasionally observed in the choroid plexus and in the white matter and the granular layer of the cerebellum. The nerve cells of the basal ganglia were pale, and many of the vessels of the

pallidum were calcified. The Dieterle-Neumann modification of the Hortega method and the Bielschowsky stain disclosed senile plaques in all parts of the cerebral cortex. The plaques did not differ in appearance from those observed in the other cases. However, they were less abundant and less uniformly distributed. They occurred with greatest frequency in the parietal lobe, the number varying from 25 to 51 per low power field (fig. 4). The cornu ammonis showed from 8 to 40, and the uncus and the hippocampal gyrus, from 5 to 45, per low power field. In the remaining parts of the cortex the number ranged from 7 to

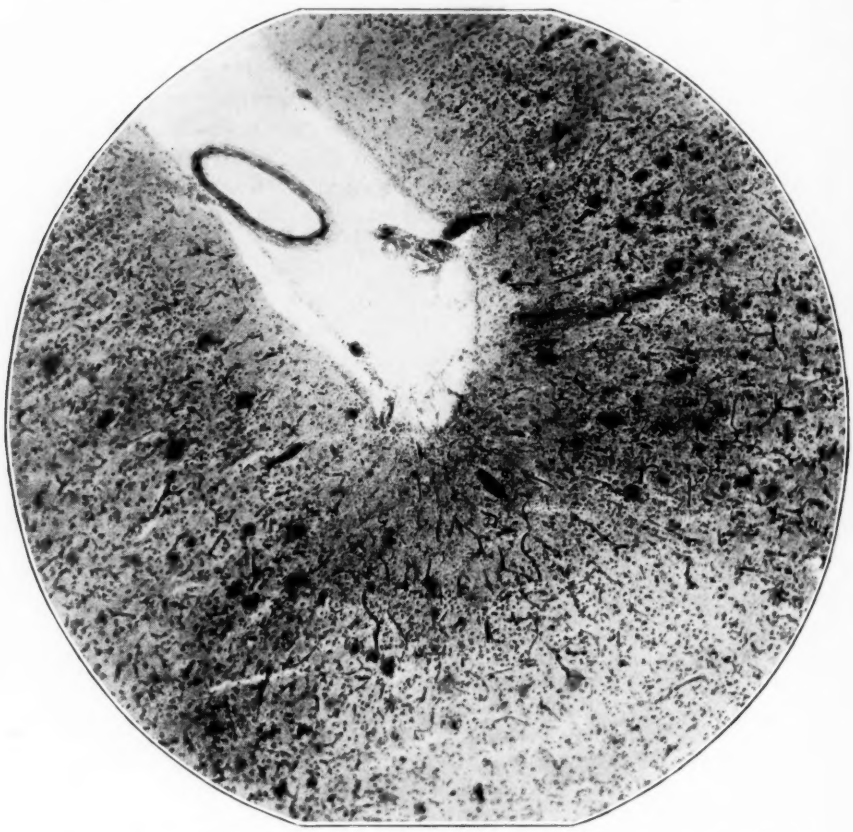

Fig. 4 (case 6).—Numerous senile plaques in the cortex of the parietal lobe. Dieterle-Neumann modification of the Hortega stain; × 45.

39 per low power field. Many of the nerve cells of the cornu ammonis and uncus presented neurofibrillar changes of the Alzheimer type. These lesions were observed in sparse numbers in the other portions of the cortex, though in some places several were observed per high power field. The basal ganglia failed to show plaques or alterations in the neurofibrils.

CASE 7.—*Cancer of the breast at 46; cancer of the uterus at 49, with subsequent amputation of the breast and hysterectomy, followed by roentgen and radium therapy. Several months later, depression, irritability and sleeplessness*

and periods of restlessness and confusion, with delusions of persecution. At the time of admission to the hospital, confusion, impairment of memory, disorientation and slight depression. The patient died two months later. Necropsy revealed carcinomatous growths in the bladder, retroperitoneal and inguinal lymph nodes, right thigh and liver. The brain showed changes in the small blood vessels and widespread neurofibrillar lesions of the Alzheimer type.

History.—I. B., a white woman, aged 50, was admitted to the Foxborough State Hospital on Oct. 2, 1933. The family history was of no significance. The patient was married; she had never been pregnant. The husband was well. The patient was described as cheerful and a good mixer. She had worked in a watch factory for many years. She had had influenza in 1918 and apparently made a good recovery. Approximately four years before her admission to the hospital, she noticed a lump in the left breast and three years later began to suffer from menorrhagia. On Dec. 20, 1932, she was hospitalized. The left breast was amputated, and a complete hysterectomy was performed. Pathologic examination disclosed carcinoma of the left breast and adenocarcinoma of the endometrium. The patient was discharged on Feb. 8, 1933, but later was given radium and roentgen treatment. She seemed well for a time but soon began to complain of general pain and aching. She became depressed, irritable and sleepless. She was admitted to the Pondville Hospital on Aug. 9, 1933, and was discharged eleven days later. She became slightly forgetful and untidy in appearance. She was readmitted to the Pondville Hospital on Sept. 24, 1933. There was tenderness over the lower end of the right femur, and examination revealed considerable atrophy of the bone, with periosteal reaction. The patient talked irrationally at times and apparently suffered from hallucinations. She was restless and confused. She expressed delusions of persecution and became so noisy that it was necessary to commit her to the Foxborough State Hospital.

Examination.—The patient was well developed and well nourished. The skin was pale. There was a large, healed operative scar in the region of amputation of the left breast and another in the lower part of the abdomen. The lower end of the right femur showed a large spindle-shaped swelling immediately above the knee. The blood pressure was 156 systolic and 98 diastolic. The pupils were sluggish in reaction to light but reacted well in accommodation. There were coarse irregular tremors of the extended fingers. The patient was confused and slightly depressed. At times her speech was incoherent. She was partially disoriented as to time and place. Memory for recent events was impaired.

Laboratory Observations.—The urine contained a very faint trace of albumin and frequent leukocytes. The Wassermann reaction of the blood was negative. Examination of the blood revealed: hemoglobin concentration 70 per cent and red cells 3,540,000 and white cells 15,500 per cubic millimeter, sugar 97 mg., nonprotein nitrogen 24 mg., calcium 10.4 mg. and phosphorus 3.68 mg. per hundred cubic centimeters.

Course of the Illness.—The patient remained in a confused state during most of her stay in the hospital. There were short periods in which she appeared to be in fairly good contact with her surroundings. Physically she grew gradually weaker. Enlargement of the liver was noted toward the end of November 1933. The patient became icteric, and the temperature rose to 101 F. She died on Dec. 3, 1933.

Gross Observations at Necropsy.—Necropsy, performed eight hours after death, revealed a small decubital ulcer in the gluteal region on the right and

firm swelling of the tissues about the lower end of the right femur. The right pleural cavity contained a considerable quantity of clear yellow fluid. The mitral valve was thickened. The lungs were somewhat edematous. There were several carcinomatous nodules in the posterior wall of the bladder, with metastases to the liver, retroperitoneal glands and inguinal lymph glands on the right. The brain weighed 1,130 Gm. The basal vessels were not thickened. There was an area of softening, about 1 cm. in diameter, on the upper surface of the left cerebellar hemisphere.

Microscopic Examination.—With the Nissl stain the cerebral cortex showed spotty loss of nerve cells, chiefly in the third layer. Small acellular areas (*Verödungsherde*) were occasionally observed. Many of the nerve cells showed chromatolysis and an increase in lipoid accumulations. The Bielschowsky stain disclosed neurofibrillar lesions of the Alzheimer type in all parts of the cerebral

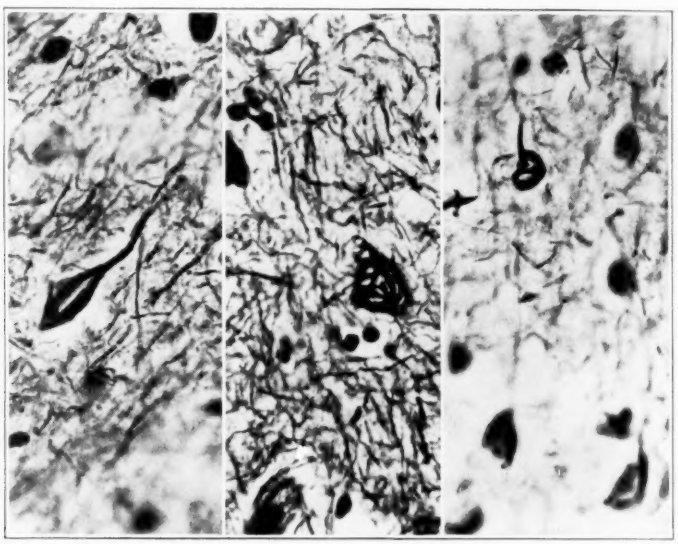

Fig. 5 (case 7).—Three cells from closely adjacent parts of the temporal lobe, illustrating different forms of neurofibrillar lesions of the Alzheimer type. Bielschowsky stain; oil immersion; × 550.

cortex. The usual variations in form were encountered (fig. 5). As a rule, the lesions were present in at least one or two nerve cells in each microscopic field. They were abundant in Sommer's sector of the cornu ammonis, which showed marked paucity of nerve cells. Some of the neurofibrils in this region were broken into small granules. The precentral gyrus and the occipital lobe presented the mildest alterations. A careful search of sections stained with the Bielschowsky method and the Dieterle-Neumann modification of the Hortega method failed to reveal any senile plaques. A considerable number of the cortical vessels showed marked endothelial swelling and proliferation. There was some formation of new vessels. The adventitia of the vessels of the pia and white matter was moderately thickened. Deposits which resembled calcium but failed to give the characteristic reaction with sulfuric acid were observed in relation to the vessels of the brain. Staining with the Turnbull blue method showed that these deposits

contained iron. With the cresyl violet stain they were highly refractile and varied from pale blue to dark violet. When Van Gieson's stain was used, they took on a brown-black tint. They were most abundant in the gray matter of the cerebellum and the parietal lobe. They occurred in the white matter as rings of small, densely packed granules in the adventitia. In the cortex they appeared as round or irregular masses located in the adventitia and perivascular spaces. It is noteworthy that these masses were always most abundant at or near the bottom of the sulci. As a rule, they predominated in the third layer. However, they were unevenly distributed, and many convolutions failed to show any evidence of the deposits. They occurred with considerable frequency about the vessels of the choroid plexus. The choroidal villi showed a pronounced increase in connective tissue.

The cases just described differed radically from the cases of the first group in spite of the histologic resemblance. There was definite evidence of toxicity or infection, which was not observed in the cases of the first group. The mental symptoms arose suddenly in direct relation to severe somatic disease. The course of the illness was rapid, leading to fatal termination within a few weeks or months after the onset of the mental disorder. The psychosis manifested itself as a state of confusion, with transient hallucinations and some loss of memory, punctuated by short intervals of lucidity. The clinical picture in both cases was, in fact, entirely typical of toxic psychosis. In our opinion, there is no justification for regarding these cases as atypical instances of Alzheimer's disease. To include cases of clearcut toxic psychosis in this group destroys the generally accepted conception of Alzheimer's disease as a distinct syndrome. While this syndrome presents considerable clinical variation, it is a fairly well defined clinical entity, a point which we wish to stress. Of course, one might speculate on the possibility that in these cases Alzheimer's disease existed in a latent form, which was accidentally discovered through the intervention of fortuitous somatic disease. However, the literature contains no reports of a latent type of Alzheimer's disease, and such an occurrence is highly improbable in a statistical sense, in view of the comparative infrequency of the disorder. As already pointed out, senile plaques and even lesions of the neurofibrils may occasionally be observed in persons of advanced age in the absence of mental and somatic illness, but to our knowledge no such cases in which there was an abundance of so-called senile alterations have been described in persons under the age of 65. The changes recorded in these cases must be regarded as an expression of the toxic psychosis with which they were associated. These cases thus provide additional proof of the nonspecificity of plaques and lesions of the neurofibrils and illustrate the necessity for consideration of the clinical picture in making the diagnosis of Alzheimer's disease.

Case 6 was of particular interest because the observations demonstrated that the complete histologic picture of Alzheimer's disease may occur independently of a senile condition. In case 7 changes in the neurofibrils only were shown and therefore the pathologic picture did not conform to that of Alzheimer's disease. Nevertheless, the case was a good illustration of the fact that a type of lesion which occurs in great numbers, chiefly in Alzheimer's disease, may be equally abundant in entirely different conditions. It is rare to see such alterations in the neurofibrils widely distributed through the cerebral cortex in the absence of plaques. The case described by Schnitzler [6] was the only one comparable in this respect to the cases which we report.

Mention should also be made of the vascular involvement of the choroid plexus in cases 6 and 7. In case 7, in addition, proliferative changes of the cortical vessels were shown of the type commonly met in toxemia and infection. This is of interest in connection with the suggestion made by Malamud and Lowenberg [13] that alterations of the blood-cerebrospinal fluid barrier may be the pathogenetic factor in the formation of plaques and lesions of the neurofibrils. According to our experience, however, pronounced damage of the choroid plexus is not observed with great frequency in Alzheimer's disease, though the small cerebral vessels regularly show hyaline-like changes and mild proliferative phenomena. These alterations do not bear any direct or constant relation to the other types of involvement, and it is impossible to determine whether they are etiologically of any importance. It is possible, at any rate, on the basis of the observations in cases 6 and 7, to state that plaques and lesions of the neurofibrils may occur in conditions which exert their influence through the vascular apparatus.

Alexander [19] was able to produce changes in the neurofibrils and argentophilia of the nuclei of nerve and glia cells by postmortem influences, such as the incubation of brain tissue in water or saline solution. He also observed similar alterations in a number of toxic and infectious disorders. He concluded that the condition in any specimen which shows changes in the neurofibrils with argentophilia of the nuclei should be interpreted only with the greatest caution and that its relationship to systemic diseases and postmortem conditions should be considered. However, these changes in the fibrils did not conform morphologically to the Alzheimer type of degeneration, and Alexander [19] stated that they could not be considered to be true examples of lesions of the latter type. Since Alexander [19] laid great stress on argentophilia of the nuclei as an indication of the "soaking change" which he described, we exam-

19. Alexander, L.: The Neurofibrils in Systemic Disease and in Supravital Experiments, with Remarks on Pseudo-Atrophy of the Brain, Arch. Neurol. & Psychiat. **32**:933 (Nov.) 1934.

ined the material described in this paper and that reported previously [14] from this point of view. In all the tissue on which the Bielschowsky stain was used, which included material obtained in ten unquestionable instances of Alzheimer's disease, some of the nuclei showed argentophilia. Contrary to the observations in Alexander's [19] cases, the neurofibrillar lesions in the preparations in our series were in all respects similar to the changes made familiar by Alzheimer [20] and many other authors. Furthermore, in all but one of the cases senile plaques were exhibited, which were not produced by the "soaking change" described by Alexander.[19] It seems likely that the nuclear changes in such cases are merely another expression of the well known tendency of various structures to take the silver stain, which has been emphasized by Spielmeyer [21] and others as a characteristic feature of the process in Alzheimer's disease and in senile conditions.

Nevertheless, the work of Alexander [19] is important because it demonstrated that artificially induced changes in the water content of the brain may lead to certain alterations in the stainability of the intracellular neurofibrils. The alterations resembled changes of the Alzheimer type sufficiently to suggest that the latter lesions may be caused by a similar mechanism operative during life. The fact that toxic disorders may produce disturbance in the water balance of the body should be remembered in this connection. One may even speculate that a similar mechanism is responsible for the formation of senile plaques. This speculation receives support from the statements of von Braunmühl,[22] who expressed the opinion that plaques develop on the basis of colloidal changes, consisting of an increasing aggregation of colloidal particles as well as processes of dehydration. Regardless of theoretical considerations, the fact remains that a toxic condition may be associated with the fully developed histologic picture of Alzheimer's disease or senile dementia. The possible implications of this will be discussed later.

GENERAL COMMENT

A better understanding of the clinical and pathologic features of Alzheimer's disease having been attempted, the problem now arises as to the position of this condition with reference to senile psychosis. The fact that it usually begins in the forties or fifties suggested to many investigators a relationship to senile conditions. It may be pointed out

20. Alzheimer, A.: Ueber eine eigenartige Erkrankung der Hirnrinde, Allg. Ztschr. f. Psychiat. **64**:146, 1907.

21. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, p. 82.

22. von Braunmühl, A.: Neue Gesichtspunkte zum Problem der senilen Plaques, Ztschr. f. d. ges. Neurol. u. Psychiat. **133**:391, 1931.

that a similar type of distribution on the basis of age is noted in such different diseases as cancer and diabetes, and yet this has not been regarded as an adequate basis for the belief that the diseases in question are direct manifestations of senility. At the same time, the facts suggest that with advancing years changes take place which tend in some way, perhaps indirectly, to favor the development of Alzheimer's disease. However, before one proceeds further in a discussion of the whole question, it is evident that some of the current views on senescence in its normal and pathologic aspects must be examined.

Senility is one of the most obscure subjects in the field of biology. Only lately has light been thrown on normal senescence by Child [23] and Růžička [24] and on the pathologic aspects of senility by von Braunmühl.[25] According to Child,[23] senescence is primarily a decrease in the rate of dynamic processes, conditioned by the accumulation, differentiation and other associated changes of the material of the colloid substratum of the organism. He was inclined to believe that the slow increase in the aggregation of colloidal particles, decrease in water content and shrinkage which occur with time in colloid solutions form the chief physical basis of aging. Růžička [26] developed this view further, showing that such colloidal changes actually take place in the living organism, and he named the process protoplasm hysteresis. Child [23] came to the conclusion that senescence is a necessary and inevitable feature of growth and differentiation, aging being merely one aspect of the developmental cycle.

The views on the pathologic aspects of advanced life vary. Simchowicz [3a] expressed the belief that senile dementia is merely an exaggeration of the normal senium. A similar idea was expressed more recently by Warthin,[27] who laid special stress on the vascular changes in old age. On the other hand, Tilney [28] advocated the theory that old age as shown in the brain is the result of life's successive and cumulative intoxications, the old brain being actually a diseased organ. Grünthal [3d]

23. Child, C. M.: Senescence and Rejuvenescence, Chicago, University of Chicago Press, 1915.

24. Růžička, V., cited by von Braunmühl.[25]

25. von Braunmühl, A.: (*a*) Kolloidchemische Betrachtungsweise seniler und präseniler Gewebsveränderungen: Das hysteretische Syndrom als cerebrale Reaktionsform, Ztschr. f. d. ges. Neurol. u. Psychiat. **142**:1, 1932; (*b*) Versuche um eine kolloidchemische Pathologie des Zentralnervensystems: Das synaeretische Syndrom als cerebrale Reaktionsform, Klin. Wchnschr. **13**:897, 1934.

26. Růžička, V.: Ueber Protoplasmahysteresis und eine Methode zur direkten Bestimmung derselben, Arch. f. d. ges. Physiol. **194**:135, 1922.

27. Warthin, A. S.: Old Age, the Major Involution, New York, Paul B. Hoeber, Inc., 1929.

28. Tilney, F.: The Aging of the Human Brain, Bull. New York Acad. Med. **4**:1125, 1928.

and Critchley [29] stated that there is more than a mere quantitative difference between senile dementia and normal old age, and Grünthal [3d] expressed the idea that there must be an as yet unknown additional factor which determines the occurrence of senile dementia.

In this connection the views of von Braunmühl [25] are of great interest. His unusual studies on senile alterations led him to conclude that they are secondary manifestations of a change to a less dispersed colloidal state, with separation into a concentrated colloid phase and a dilute watery phase containing little colloid. He expressed the belief that clinically definable disease appears when these changes occur in systems that have become impaired. He emphasized the point of view that such changes are not exclusively the primary feature of aging but represent a general type of tissue reaction which can be caused by a variety of exogenous and endogenous factors.

While these views are still somewhat speculative, they seem to provide many clues to an understanding of Alzheimer's disease and senile conditions. The gradually increasing change from a highly dispersed to a less dispersed state of the colloids, which takes place with mounting age, may perhaps represent the increasing predisposition to Alzheimer's disease that one sees with advancing years.[30] The gradual advance of this uncomplicated process in an otherwise undamaged brain leads to the phenomena of normal old age. Senile psychosis results from exaggeration and modification of the process caused by constitutional or acquired cerebral impairment of a certain type. Alzheimer's disease must be based on a special factor or factors which are, in all probability, qualitatively as well as quantitatively different from the factors operative in senile dementia. These factors may not necessarily be the same in all cases, though the brain reacts to them in the same general way. Empirical studies lend support to the belief that Alzheimer's disease is a syndrome which may occur under a variety of circumstances. Thus, Lowenberg and Waggoner [31] observed the familial occurrence of the disease, which suggests that inheritable defects are determining factors in certain cases. One of us [12] has pointed out previously that toxic influences appear to be of etiologic significance in a few instances of genuine Alzheimer's disease. In the last two cases described in this paper it was shown that toxic conditions can be associated with a tissue

29. Critchley, M.: The Neurology of Old Age, Lancet **1**:1119, 1931.

30. One may speculate that this colloidal change may even be responsible for the increased frequency with which certain somatic diseases occur in elderly life. However, discussion along these lines is beyond the scope of the present paper.

31. Lowenberg, K., and Waggoner, R. W.: Familial Organic Psychosis (Alzheimer's Type), Arch. Neurol. & Psychiat. **31**:737 (April) 1934.

reaction similar to that seen in Alzheimer's disease and senile dementia. Such observations naturally raise the question whether Alzheimer's disease and senile dementia may be based on as yet unrecognized toxic factors. As a fact, it is known that senescence in certain lower organisms can be greatly influenced by changes in diet (Child [23]) and by hunger and endocrine factors (Růžička [24]). Thus, the conclusion is reached that the aging process, which is inherent in living organisms, may be modified and altered by different factors and that it is these factors that lead to different diseases or syndromes. Not much is yet known about these factors, but it seems to us that the line of approach outlined in this paper provides a fertile field for future study.

Finally, it may be pointed out that psychologic aspects of Alzheimer's disease and senile conditions still need elucidation. We wish to call attention to certain psychologic features which can perhaps be correlated with the physical changes detailed in the preceding paragraph. Thus, normal senility is associated with regression to a childish type of behavior, which is expressed by the term "second childhood." In senile dementia there are more primitive modes of behavior, which indicate regression to more infantile levels of functioning. In Alzheimer's disease there is a similar lowering of function, but, in addition, the patients seem to react more vigorously to the disease. The regression is in some respects more profound than that usually noted in senile dementia. The more vigorous reaction to the disease may be based on the fact that younger persons are involved. The patients struggle against the illness and do not accept it passively. Even a casual review of our material disclosed strong personal factors in the earliest stages of the illness in three of the five cases. Such factors can be interpreted as an early indication of the struggle against the oncoming disease. The marked motor unrest and some emotional changes may be regarded as exaggerations of certain infantile traits. These features can be classed as compensatory reactions in the sense used by White.[32] The principle of compensation is well known in medicine and has been widely applied to somatic as well as to psychic processes. White [33] has pointed out that one has a right to ask: What is the significance of the disease for the patient? We postulate in answer to this question that in Alzheimer's disease there is an attempt at rejuvenescence in the face of an abnormal aging process.

A biologic basis for this view may perhaps be seen in the work of Child,[23] who regarded senescence and rejuvenescence not as special

32. White, W. A.: The Social Significance of Mental Disease, Arch. Neurol. & Psychiat. **22**:873 (Nov.) 1929.

33. White, W. A.: Medical Psychology: The Mental Factor in Disease, Nervous and Mental Disease Monograph 54, Washington, D. C., Nervous and Mental Disease Publishing Company, 1931.

processes but as certain aspects of the physicochemical changes constituting life, which go on side by side, one dominating the picture whenever it fails to be balanced or overbalanced by the other. At the same time, we realize that the aforementioned considerations are still largely speculative. They are advanced as suggestions for future investigation, and as such we believe that they may be of value in providing new angles of approach to problems of psychiatry and neuropathology that are still poorly understood.

SUMMARY AND CONCLUSIONS

Five cases of Alzheimer's disease are reported.

The clinical picture may vary considerably in different cases, but the disease may be regarded as a fairly well defined clinical entity.

Pathologically, Alzheimer's disease shows widespread cortical damage, the chief features of which are nonspecific cellular changes, senile plaques and neurofibrillar lesions of the Alzheimer type. Involvement of the basal ganglia is common.

Two cases of toxic psychosis are reported in which lesions of the type occurring chiefly in Alzheimer's disease and in senile disorders were shown. In one of these cases the fully developed histologic picture of Alzheimer's disease was presented. These observations, taken in conjunction with others recorded in the literature, support the view that the changes characteristic of Alzheimer's disease and of senile conditions represent a general type of tissue reaction which may be caused by different exogenous and endogenous factors.

In an attempt to determine the relationship between Alzheimer's disease, senile dementia and normal senescence, the current views on senility are reviewed. The conclusion is reached that the aging process, which is inherent in living organisms, may be accelerated, exaggerated or modified by various factors. These factors lead to the different diseases or syndromes which appear as pathologic manifestations of the aging process. The question is raised whether toxic influences play a rôle in the origin of Alzheimer's disease and senile dementia.

From a psychologic standpoint Alzheimer's disease is characterized by profound regression to primitive infantile levels of behavior, with a tendency to compensatory phenomena. The suggestion is made that one is dealing with an attempt at rejuvenescence in the face of an abnormal aging process.

FEELING OF UNREALITY

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Since the first description, by Krishaber [1] in 1874, of the syndrome of unreality, many observers have amplified the available knowledge with case reports, but the number of psychoanalytically investigated cases in which the feeling of unreality or depersonalization is the predominating symptom remains small. The feeling of unreality occurs occasionally in persons whose general psychic integration is not affected by the transient experience.

Neither the feeling of unreality nor the circumscribed phenomenon of depersonalization is a morbid entity, although the depersonalization may be sufficiently prominent to dominate thoroughly the psychiatric picture. A feeling of unreality may persist for a long time, and the patient may describe himself as "walking death" or a "living shadow." On the other hand, the feeling may alternate with reality in veritable waves, registering the change thirty or forty times within an hour.

The distinguishing characteristic of the symptoms in the syndrome of the feeling of unreality is that the patient retains his grasp concerning and insight into the abnormality. Whether he complains that he himself seems unreal or that the outer world seems unreal, the integrity of his critical evaluation of the change is not affected. The unreality is something deviating, irritating and alien. In this he differs from the schizophrenic and the depressed patient of the manic-depressive group, although complaints of the feeling of unreality are commonly made by patients of both types.

The feeling of unreality arises involuntarily, and it is usually beyond the power of the patient to control its appearance or to dispel it. Many patients seek to combat it and are likely to indulge in some device involving the thinking process, such as reading or working out mathematical problems. The presence of fatigue or exhaustion did not, in my series of cases, precipitate the feeling or prolong its duration when it had already occurred. Usually the change to the feeling of unreality is extremely painful. One patient described it as a feeling of being torn apart when it occurs. "I am no longer Mrs. G.; I am not real. When

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Read before the American Psychiatric Association, Washington, D. C., May 15, 1935.

1. Krishaber, M.: De la nevropathie cérébro-cardiaque, Paris, G. Masson, 1873; cited by Hesnard, A.: Les troubles de la personalité dans les états d'asthénie psychiques, Paris, Felix Alcan, 1909.

unreality occurs at home, it is painful, but on the street unreality is torture." While the transition from one state to another is distressing and annoying in all instances, some patients have reported that when they are unreal they are irritable and easily annoyed and have the desire to be alone.

Among persons who seek psychiatric aid, feelings of unreality are found in association with conditions which can be classified either in the group of the psychoneuroses or with the psychoses. In the eight cases which I have studied psychoanalytically at various times during the past fifteen years, the diagnosis of psychosis would have been considered by most psychiatrists in four cases—schizophrenia in two and a condition allied either to manic-depressive psychosis or to schizophrenia in two cases. In the other four the condition could have been fitted into several diagnostic groupings, depending on which factors were most emphasized. I regarded them as instances of neuroses. The presence or absence of the feeling of unreality affords little satisfaction to those psychiatrists to whom classification is reassuring.

States of unreality are closely associated with thought block, feelings of stupidity, fugues, dream states and other types of involuntary withdrawal, the most extreme forms of which may show loss of consciousness. An interesting allied state is that in which the patient appreciates situations intellectually but experiences no emotion with his thinking. There is an absence of "inner feeling or pleasure," which the intellect "tells" the patient is a sick state, but the solace obtained from his symptom of intellectualizing prevents him from taking any steps toward a cure.

In my experience the phenomena in the depersonalization category occur more often in women than in men (six cases in women to two in men in a clientèle over 60 per cent of whom are men). Yaskin [2] reported that of mild mental depressions in which the feeling of unreality was a constant symptom, 67.9 per cent occurred in women. Such a preponderance in women corresponds with the theory that depersonalization depends on an identification of the patient with the parent of the opposite sex, who happens to personify intellectuality to the patient. Many women entertain the concept that men think more profoundly, more logically and more successfully than persons of their own sex. Attempts to attain the masculine type of thinking predisposes, as was pointed out in a previous paper,[3] to the eroticization of thought under certain circumstances. The association of eroticization of thought in depersonalization has been noted by several observers, particularly

2. Yaskin, Joseph C.: The Feeling of Unreality as a Differential Symptom of Mild Depression, Arch. Neurol. & Psychiat. **33**:371 (Feb.) 1935.

3. Oberndorf, C. P.: Depersonalization in Relation to Eroticization of Thought, Internat. J. Psycho-Analysis **15**:271, 1934.

Hesnard, who was quoted by Morgenstern.[4] The latter even spoke of the "male intelligence" of the woman in one of the cases she reported.

It is also possible for a boy to identify intellectuality as a feminine trait and to repress the function of thinking in later life as a characteristic incompatible with his sex. The sequence, narcissistic wound caused by the rebuff from the "stupid" parent, identification with the thinking parent, subsequent eroticization of thinking and repression of the eroticized thinking function as incompatible with biologic rôle, lays the foundation for the symptom in the general category of depersonalization.

REPORT OF A CASE

The patient whose case is to be reported presented the symptom that what was occurring in the world did not interest him and he could not be affected by it. The feeling had persisted for ten years. This partial psychic paralysis had nullified his college course and constituted a real threat to his business efficiency. The direct expression of the feeling of unreality, present when he was in the company of girls, was not as pronounced as that in other cases I have studied.

History.—The patient, business manager of a literary organization, came for treatment at the age of 33 because of vacillation in regard to marriage. In addition, he suffered from fears of jumping out of the window, of skidding in an automobile and that his razor might fall on his phallus while shaving, thereby injuring or amputating that organ. Another symptom was that in his conversation with girls he seemed unreal and foolish to himself.

The patient was born of Jewisn parents in a hamlet in Northern Texas, where his father kept a small country store. He had a sister four years older and a brother four years younger. Always puny and undersized and handicapped by poor eyesight, the patient began early to use his mind as a justification for his retirement from boys' games and as a compensation for his inability to cope with more vigorous children in the small Christian village.

His parents, who, as is nearly always the case, furnished the model of superego formation, possessed characteristics which led to the clash of identification. The father was a retiring man, possessed of little energy, who spent his time in the rear of the small store while his wife attended customers in the front. The mother represented the activity and self-reliance which conformed with the standard of masculine endeavor of northern Texas, a pioneer frontier at the time when the patient grew up. The sedentary father, with his intellectual pursuits, seemed a contemptible inferior to the patient. These opposite tendencies of father and mother were never reconciled in the patient's mind.

When the patient was 18 months old, a trauma in the form of an early disappointment in his mother took place. He was born in April, and it was customary in the locality to nurse a child for one year. To avoid the risk of weaning during the summer months he was kept at the breast until he was 18 months old. The mother verified a vague impression which the patient carried in connection with

4. Morgenstern, Sophie: Psychoanalytic Conception of Depersonalization, J. Nerv. & Ment. Dis. **73**:176, 1931.

this weaning. He reacted so vigorously against the change to the bottle that she attempted to discourage suckling by smearing her breast with lamp-black and offering it to him. He did not balk in the least. The next time she offered him the natural nipple covered with a quinine solution. It cured him of desire for the breast.

Again at the age of 3, when his mother rejected his plea for sympathy when he was mildly hurt, the patient definitely realized that he had little to expect from her in this direction. Nevertheless, the attachment to her and to his older sister as a substitute continued frankly sexual. It included an actual attempt at incest with his sister at 14 and sexual dreams manifestly involving his mother when he came for treatment. Adolescent masturbation began at the age of 12 and continued intermittently up to the time when he began treatment. It was mechanical and singularly free from erotic fantasy.

Rebuffed by his mother, the patient early began to apply himself energetically to his studies. In the grammar grades he was an exceptionally good student, intensely concerned with doing good work. This was partially due to a desire to be well liked by the teacher and to force the boys with whom he could not compete in games to respect his mind. In his last year in grammar school he had the highest marks attainable in every subject. During this period he noted a peculiarity in himself—when writing examination papers he could not decide to hand them in. Apparently the delay tended to heighten excitement to a great degree and caused pleasurable stimulation about the genitals, of which the patient became acutely conscious.

During the high school period also the patient was an excellent student, although he did not show the extraordinary performance which he had shown in grammar school. He interested himself in outside activities of a literary nature and became an outstanding figure in school journalism, debating and dramatics. Especially in his junior and senior years, the feeling developed that he was respected by the student group, although he never felt that he had become a member of it.

Even before entering high school the patient distinguished himself as a speaker. In high school he experienced no difficulty in becoming one of the best debaters and was chosen to represent northern Texas in an interstate debate held in a neighboring city. The make-up of both debating teams was masculine. While he was delivering his speech, he suddenly had the conviction that he had urinated and that the fluid was dripping down the left leg of his trousers onto the stage. The sensation was vivid and real, but he continued to speak. From that moment it was as though some one else were doing the talking. His voice sounded far away, and he ceased to exist as a person, though he did finally finish his speech. As he said: "The real I was worried about having urinated on the floor; the shadow gave the talk." When he returned to his chair on the platform, observation of himself revealed that no such accident had occurred. He experienced a great sense of relief, and gradually his personality returned. Of course, no one in the audience realized that a depersonalization had occurred, and his speech was extremely successful.

One year later, in a state oratorical contest, a similar thing occurred. The patient suddenly had the feeling of "giving out." His voice became flat and colorless, and he became conscious of it. The debating coach subsequently asked him what had happened, for the change in his manner became apparent. Through his hollowness he lost first place, which both he and the coach knew would have been awarded him had he remained himself.

The patient's college life was a total waste of time: There was a significant lack of activity, both mental and physical, which was extremely alien to him. He

felt that he did not belong there and that the situation was empty and vacuous. Indeed, he had no desire to go to college, but his mother shipped him away to the University of Kansas, where he spent a meaningless year. He is inclined to attribute this to war time conditions: The student army corps was active, and he felt entirely anomalous in the semimilitary life of the state university. His feelings of masculine inferiority were constantly touched. The year at the University of Kansas had been so empty to him that he did not wish to go back, but again his energetic mother sent him away, this time to Yale University. Here a feeling of bewilderment and inferiority persisted throughout the three years. He thought that the reason he made no effort to do well in his studies or to distinguish himself on the campus was that there were no women in college and that he felt he should not have been studying but out making a living for his mother.

The symptom of delay which the patient first experienced in connection with examination papers continued to be a minor but annoying symptom in two situations. It deprived him of two recreations which are valued social assets in his set—golf and bridge. When he is on the tee, there is an interminable delay in hitting the ball which invites all sorts of sarcastic criticism from his fellow players. Similarly, in bridge he suffers from indecision in a mental way—he cannot play quickly, so that the other players constantly make him the butt of their remarks.

Analysis.—The facts in the life history of the patient afford significant data of his early rejection by the mother and the tendency in boyhood to identify study and "head work" with the father. This emphasis on study as masculine served to justify it as a refuge for the weak youth, whose poor vision and scrawny body precluded participation in the games of boys. His physical defects did not prevent the development of the usual infantile incestuous attachments to mother and sister. As long as he could use his mind for attaining distinction, it satisfied his libidinal strivings.

The first evidence of failure of sublimation in the use of his head became apparent when, at the age of 10, the symptom of sexual excitement developed—when he delayed in handing in examination papers. This delay is the first evidence of indecision. A thought is action not carried to completion. Continued thinking represents delayed action, but the stimulus of thought and that of action are identical. The boys in the country school finished their papers quickly and, with an irresponsibility which seemed enviable to the patient, rushed from the classroom to play their rough games. Some of the girls would remain behind even at recess time. The patient remained in, thinking, which was accompanied by pleasurable genital feelings, undecided as to whether he should act and be a boy or stay in the school room and be classed as a "girl."

This symptom of delay has shown itself in the patient's playing bridge in a manner which he thinks is identical with the examination paper experience—it is indecision in a mental way. He cannot play quickly because he wishes to show his male opponents that he has a good mind, but exhibiting his mind is demonstrating the tendency which

is only half masculine because of his identification of thought with the feminine father and of activity with the masculine mother. To the average man the demonstration of mental capacity (quick, clear thinking) would be an exhibition of masculinity in a full sense to which there would be no need of inhibition and no tendency to repression. His delay in showing his mind is a plea to the other men that he is only 50 per cent masculine, and for that reason the men should have patience with him and treat him nicely. He has summed up his indecision as being perhaps three-eighths a desire to show his masculinity and five-eighths an appeal to his male fellow players to sympathize with him as a woman. Notwithstanding the knowledge that he is not a good player, he enters a game in the unconscious hope that the other men will "jump on him," that is, treat him roughly as a woman.

The close relationship between the delay in playing bridge, so reminiscent of the delay in the examination paper, and a tantalizing delay in hitting a golf ball on the tee is also striking. It can be interpreted as indecision as to whether the patient should walk out among the men, which striking the ball would compel him to do, or stay back alone like his father in the rear of the store. But even this indecision is preceded by an earlier indecision as to how he will act if he actually gets on the fairway.

More specifically, the delay in his stroke in golf is greater in drawing back the club than in the swing forward, which is too quick. This may be considered as an unconscious desire on the part of the patient to withdraw, which the masculine super-ego forbids, causing the hesitation. The quick forward swing is probably an overcompensation for the time wasted in withdrawing.

In the oratorical contest in which the patient was compelled to speak on the masculine debating team, he felt that he spoke as a "masculine woman"—merely reading and spouting, not thinking—making a spectacle of himself as a "talking girl." At the behest of the masculine super-ego it became necessary for him to repress this feminine component, changing his personality and leaving it empty and hollow. The feeling that he urinated before the assembled audience was an expression of the unconscious wish to demonstrate in the most effective way that he was not merely an orally aggressive woman but a man who urinated standing.

The analysis of a dream of the patient tends to verify the significance of the symptom of delay. "I am at a railroad station, like a subway station; I see a news and candy stand. I decide I would like some candy. I am selecting candy when the train is preparing to leave the station, and I have become aroused for fear that I shall miss the train. I keep trying to make a selection of one package of candy, although I realize that every second counts. I get more and more worked up; it is all mental. It is

a dangerous thing I am doing in delaying, but it is delicious to linger over the choice. The train leaves the station. I wake up with an ejaculation." [5]

The patient appreciates in his feeling tone in the dream a close analogy between the delay in school and the delay in the railroad station. He thought that in the school room situation he was defying the teacher, whereas in the train dream he is defying the train, which seems like the teacher—constantly admonishing him to come on, to hurry up.

It has always been one of the patient's weaknesses to buy candy, and to him the indulgence in sweets has always represented something distinctly feminine. Whenever he overcomes this desire, he feels stronger and more manly.

Delay is due to his indecision, which is essentially thinking alternatingly in the affirmative and negative, a mental movement back and forth in which using his head seems to equate a demonstration of masculinity which expresses itself through physical ejaculation. Here too continuation of thinking is delayed action, and in this case choosing candy represents thinking (masculinity), which in turn prevents him from catching the train, namely, action (femininity), but the thinking terminates in direct sexual expression.

When the patient was plunged into the strictly masculine environment of the university, he found himself paralyzed by a conflict of choice of rôles. He could not participate actively even in the literary field, because all action was associated with femininity, which would be out of place in a collegiate man's world (repressed identification with the active mother, that is, the masculine woman). On the other hand, he could not study, because to him study was the characteristic of the feminine man. Again he must avoid this normal university endeavor as an indication of femininity. Repression of the feminine component which was related in his case to both activity and study put him in a helpless position in which the things which went on about him in the

5. Another patient, with strong unconscious homosexuality, suffering from the feeling of unreality (Internat. J. Psycho-Analysis **16**:296 [July] 1935) reported that she felt a "pleasurable danger" when she was about to do something, but delayed to the last moment. The feeling was associated with getting into, or rather not getting into, a bus or street car. She waited until the last minute and then climbed on hurriedly. The danger lay in the possibility that she might spoil the pattern of her accepted life by not being or going where she had planned.

During such a time of delay she experienced an actual physical sensation in the vagina and vulva. It caused a loosening of the vulva and secretion in the vagina which resembled the sensation of the beginning of an orgasm. Because the sensation was self-induced it was more pleasurable and exciting. The feeling was also akin to urination; a complete relaxation of all the related muscles. The patient felt "limp, like urinating and masturbating." The whole was an exquisite feeling, very much like an orgasm but more satisfying.

university did not concern him. He could do nothing, for whatever he might do was intolerable to the conflicting, evenly contending components (super-ego category) of his mind. From the pregenital interest in weaning it would be possible to formulate the patient's conflict in terms of oral receptive and oral sadistic polarities.

The analysis of these unconscious factors enabled the patient definitely to associate activity with masculinity and to dissociate intellectual endeavor from femininity. As a result he found himself able to follow his desire to wed, and at the time of writing he has been happily married for a period of over three years. It has also enabled him to use his mind relatively fearlessly in his contacts with his employees and with other men. The feeling of disinterest in what goes on in the world caused by the conflict of two contradictory super-ego tendencies is almost absent.

In this as in other cases of patients suffering from unreality, the feeling of stupidity, or depersonalization, the symptom of unreality is one of the severest obstacles which can be opposed to the acceptance of the analyst's aid. What one part of the personality hears and appears to accept never reaches the other part, or because of the feeling of unreality, what is said appears to be irrelevant to the patient. While the meaning of the analyst's words is clear and intelligent, their significance has no pertinence for the patient and falls on an impervious partition.

COMMENT

While analyses of cases of depersonalization are few, many theories have been propounded. Most of these have emphasized the withdrawal of libido from the object and its utilization in self-observation. (A bibliography of this topic is appended to the articles by Oberndorf [3] and Morgenstern [4]).

Freud expressed the theory that in cases of multiple personality identifications have been formed with various persons which cannot be harmonized with one another. This concept antedates the formulation of the concept of the super-ego, which is considered to develop as a result of parental or parental surrogate identification. The thesis of this communication is that in the feeling of unreality the presence of a bisexual conflict is essential, with repression of the type of thinking considered by the patient to be characteristic of the opposite sex. He may then overinvest the preferred type of thinking with much of the libido which would normally have been attached to the rebuffing parent.

The idea of masculine and feminine types of thinking and action is widespread among persons of various cultural and educational levels but may appear too vague for scientific application. The characteristics of the two types are difficult to define or to delimit. But their existence is a real and potent concept to this class of patient. What

constitutes the characteristics of either type may not be the same precisely to any two patients, but the patient associates them as a quality of the favored parent. This does not necessarily mean that the concept would conform to what other persons would include under the phrase a "masculine" mind or a "feminine" mind. The patient makes the identification through a purely individualistic process.

Freud [6] in 1919 considered and rejected the theory that the origin of the process of repression lay in bisexuality. He also at that time rejected the theory that the masculine protest could be the cause. The clinical observation in this and in other cases indicates that the origin of repression may be a conflict of a bisexual nature which develops in response to clashing identifications in the super-ego.

Certainly the feeling of unreality is far more prevalent in neuroses than is ordinarily recognized. The striking alteration from reality to unreality as a specific reaction occurring only in the presence of male, female or mixed company often furnishes a clue to the origin of the conflict. Embarrassment and confusion in society are due to the circumstance that the super-ego cannot decide which sexual rôle it will allow the ego to assume. Such uncertainty of conduct and social awkwardness are particularly noted at the age of puberty, when definite assumption of sociosexual rôles is demanded by society. In this connection it is pertinent that Leroy,[7] on the basis of a questionnaire on depersonalization and *fausse reconnaisance,* found both symptoms to be a frequent manifestation at the time of puberty.

Further, it seems likely that the increase in psychoneuroses over hysterical conversions in civilized society, in which such high value is placed on thinking, is associated with eroticization of thought. With ever widening culture it has become necessary for man to repress both his conscious and his unconscious sadistic impulses, which have probably not diminished appreciably for many centuries. They are more likely to take the form of thinking than of action. Conflicts dependent on repressed sadism expressed in the form of neurosis are constantly increasing. The greater libidinization of thinking and the expression of conflict in terms of the function of a libidinized organ may account for this change.

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6. Freud, Sigmund: Ein Kind wird geschlagen, Internat. Ztschr. f. Psychoanalyse **5**:169, 1919.

7. Leroy: L'illusion et fausse reconnaisance, cited by Störring, Ernst: Die Depersonalisation: Eine psychopathologische Untersuchung, Arch. f. Psychiat. **98**:462, 1933.

INSULIN HYPOGLYCEMIA IN EPILEPSY

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WITH THE TECHNICAL ASSISTANCE OF

RUTH BOLTON, A.B.

LOS ANGELES

In this study epileptic patients were given injections of insulin for the purpose of determining the rôle of hypoglycemia in precipitating seizures. Reports of many studies have appeared in the literature suggesting that epileptic attacks may be due to hypoglycemia. On the whole, the evidence has been indirect and not conclusive. Recent clinical knowledge of hyperinsulinism and other types of hypoglycemia has aroused attention anew to this problem. Harris [1] reported three cases of hyperinsulinism and collected reports of twelve others (twelve of fifty recorded cases) in which convulsions were the predominant symptom. In several of these cases a diagnosis of epilepsy was made at first.

The injection of insulin is known to induce convulsions in several species of animals. In fact, insulin was formerly assayed in rabbits by this method. Convulsions resulting from an overdose of insulin are of infrequent occurrence in adult human beings. Still, if hypoglycemia bears any etiologic relation to the seizures of epilepsy one would expect insulin to produce convulsions in these patients more readily than in normal persons. Indeed, the direct induction of hypoglycemia in a group of epileptic patients might present the crucial evidence necessary to a solution of the problem.

MATERIAL AND METHODS

The patients studied included forty-two men and women, between the ages of 16 and 40 years, who attended the outpatient departments of the Los Angeles County General Hospital and the Cedars of Lebanon Hospital. In one half of these no etiologic agent was apparent. The conditions of the other twenty-one were diagnosed as follows: cerebral trauma, six; acquired syphilis, five; encephalitis, four; alcoholism, two; psychoneurosis, two; narcolepsy, one, and an "organic" condition, one. The average number of convulsions in this group was approxi-

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1. Harris, S.: Epilepsy and Narcolepsy Associated with Hyperinsulinism: Report of Three Cases of Epilepsy and of One Case of Narcolepsy Cured Clinically by Partial Resection of Body and Tail of Pancreas, J. A. M. A. **100**:321 (Feb. 4) 1933.

mately four per month. If, however, one omits three patients having thirty, thirty and twenty seizures per month, respectively, the average becomes two per month.

Three groups of experiments were conducted. Originally insulin alone was given to patients. Since the results were not striking, superhydration was produced in addition to the administration of insulin. Hypoglycemic phenomena occur more readily in animals given an overdose of insulin when, in addition, large amounts of water are administered.[2] Since hydration alone is known to influence the frequency of convulsions, a third series of experiments, in which water alone was administered, was indicated. Although it was planned to perform all three tests on each patient, this was not accomplished, since some patients failed to return after one or two of the tests. Hence there were forty experiments in which insulin alone was used, thirty in which insulin and water were used and thirty-one in which water alone was used. The total number of studies was one hundred and one. Of this number, sixty-six served as a control group in that all three tests were done on each of twenty-two subjects at approximately weekly intervals. The sequence of tests was changed with successive patients.

Insulin containing 40 units per cubic centimeter was injected subcutaneously in doses of from 10 to 60 units. Specimens of blood for determination of the sugar content [3] were taken preceding the injection of insulin and at hourly intervals thereafter for three or four hours. The blood was oxalated, and a Folin filtrate was prepared within thirty minutes. Observations extending over the same period were recorded of the pulse rate, temperature, blood pressure, tremor, perspiration and dilatation of pupils, together with other symptoms of hypoglycemia. The symptoms were terminated at the end of the test with the administration of orange juice and dextrose by mouth.

The patients in whom superhydration was produced drank 7 quarts (7.7 liters) of water at the rate of 1 quart (1.1 liters) in each thirty minutes. Those receiving both insulin and water commenced drinking immediately after the injection of the insulin. At the beginning of each test the subject emptied his bladder, and the urinary output was noted for the four hour period of observation.

In all except five tests the patients were in a preliminary period of fasting. One-half were without food for thirty-six hours and the other half for twelve hours (overnight). The longer period of fasting was utilized to secure a partial depletion of glycogen stores so as to obtain a more uniform blood sugar level. This procedure tended also to exclude any cases of spontaneous hypoglycemia. However, fasting is said to prevent the occurrence of convulsions. Therefore, the overnight period of fasting was tried in one half of the experiments.

RESULTS

The pertinent data on one hundred and one tests are summarized in table 1. No convulsions occurred with the administration of insulin alone; four occurred with the administration of water plus insulin, and four, with the administration of water alone.

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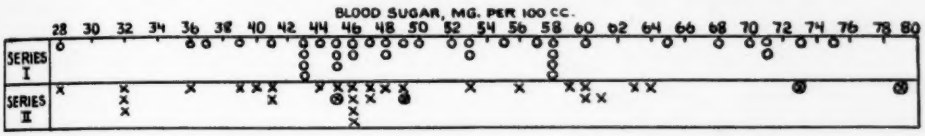
2. Moracci, E.: Concerning Convulsions in Pigeons Arising from Substances Lowering the Blood Sugar: I. Investigation of the Factors Determining the Onset of Convulsions, Boll. d. Soc. ital. di biol. sper. **7**:302, 1932. Drabkin, D. L., and Shilkret, H.: Insulin Anhydremia: Importance of the Water-Reserve in a Physiologic Crisis, Am. J. Physiol. **83**:141 (Dec.) 1927.

3. Benedict, S. R.: The Estimation of Sugar in Blood and Normal Urine, J. Biol. Chem. **68**:759 (June) 1926.

Insulin.—The conspicuous finding was the absence of convulsions in patients receiving insulin alone, even though the blood sugar level in one case was as low as 28 mg. per hundred cubic centimeters. The hypoglycemia induced was in most instances of pronounced degree and of long duration, often for two or three hours. It is usually stated that convulsions due to insulin may develop when the blood sugar level is 45 mg. per hundred cubic centimeters. In thirteen of the forty tests (series 1) the hypoglycemia reached this level or lower (chart). The lowest blood sugar readings were near to actual zero since the nonfermentable reducing substances in the blood—from 20 to 30 mg.—must be subtracted from the determinations by the Benedict method. The amount of these substances is not affected by insulin.

The hypoglycemic symptoms in these patients were of interest. Mild symptoms of an overdose of insulin, e. g., dizziness, weakness, hunger, tachycardia, increased pulse pressure, tremor, perspiration and somnolence, were present in almost every case. The pulse rate was not altered in eighteen cases; it was increased more than 10 points in sixteen cases and decreased by more than 10 points in ten cases. The average number of units of insulin per case for these groups were 36, 40 and 46, respectively, revealing a tendency for the higher doses to produce bradycardia. The pulse rate may increase at one stage of hypoglycemia and decrease at another during the same test. These reactions on the pulse rate are hardly in conformity with the theory that hypoglycemic symptoms are due



The blood sugar levels in patients receiving insulin. The circle indicates the cases in which insulin alone was given; the cross, the cases in which insulin plus water was given, and the cross within the circle, the cases in which convulsions occurred during the test.

to stimulation of the adrenal glands, unless one postulates that early there is a sympathetic or epinephrine effect and later a parasympathetic or vagotonic effect. An increase in pulse pressure was the most sensitive hypoglycemic factor noted; it occurred even when the blood sugar content decreased but slightly. Tremor also was one of the most generally present early signs. Pupillary dilatation did not appear in any of the patients. Perspiration, when present, was a prominent and trustworthy sign of hypoglycemia. After the larger doses of insulin there was marked hypothermia. In one instance the temperature was 94 F. (95 F. by rectum). The temperature varied between 97 and 94 F. in thirteen of fifteen cases in which it was recorded. Pronounced mental symptoms occasionally resulted, including inability to concentrate, inability to perform simple mathematical problems, negativistic states and marked confusion.

Insulin Plus Superhydration.—Convulsions occurred during the period of observation in four of the thirty tests in which superhydration was produced in addition to the administration of insulin (series 2). The striking feature in these tests was the presence of seizures when the blood sugar values were high and their absence when the values were very low (chart). The blood sugar readings in the cases in which convulsions occurred (cases 20, 33, 50 and 85) were 45, 77,

TABLE 1.—*Summary of Observations in One Hundred and One Tests* *

Number of Experiment	Initials of Patient	Date	Diagnosis	Hours of Fast	Units of Insulin	Liters of Water	Blood Sugar Readings					Postobservation Convulsions
							Fasting	1st Hour	2d Hour	3d Hour	4th Hour	
A. Patients with Convulsions During a Four Hour Period of Observation												
20	F. L. P.	4/ 5/34	I	36	25	4	71	45	C	..	..	
21	F. L. P.	4/12/34	I	36	..	5	..	..	..	..	..	
32	R. G.	4/23/34	I	36	25	5½	118	59	77 C	59	..	
33	R. G.	5/ 7/34	I	36	..	5	...	..	C	..	..	
34	R. G.	5/21/34	I	36	25	..	105	74	..	75	..	
48	S. McD.	5/16/34	T	36	..	7	...	..	..	..	..	½ hr.
49	S. McD.	5/28/34	T	36	40	..	83	52	64	57	67	
50	S. McD.	6/ 4/34	T	36	40	5	93	61	71	C	..	
51	M. H.	5/18/34	I	36	..	5½	...	..	..	C	..	
82	P. A.	7/ 9/34	A	12	..	6	100	..	92	..	62	
83	P. A.	7/17/34	A	0	..	7	93	78	75	33	91	
84	P. A.	7/23/34	A	12	60	..	105	44	56	53	..	
85	P. A.	7/31/34	A	12	60	3	95	49	C	..	..	
89	A. S.	7/12/34	I	12	..	4	59	..	66	C	..	
90	A. S.	7/17/34	I	12	35	..	83	64	59	50	48	
91	A. S.	7/26/34	I	12	35	5	98	61	45	32	50	
95	J. B.	8/13/34	L	12	..	7	..	..	..	C	..	
B. Patients with Convulsions Within Eight Hours After Observation Period												
18	M. S.	4/11/34	I	36	..	4	..	..	..	..	..	
19	M. S.	4/18/34	I	36	20	5	98	56	57	62	..	2 hr.
35	W. R.	4/25/34	I	12	30	7	92	60	73	74	..	
36	W. R.	5/ 7/34	I	12	..	7	..	..	..	..	..	1 hr.
37	W. R.	5/10/34	I	36	32	..	87	53	50	54	46	
38	W. R.	5/17/34	I	36	30	7	78	43	57	47	..	
39	J. S.	5/11/34	T	36	35	..	78	43	57	47	..	
40	J. S.	5/18/34	T	36	35	7	125	36	..	48	54	½ hr.
41	J. S.	5/25/34	T	36	..	7	79	..	..	..	88	
45	S. I.	5/24/34	L	36	..	7	80	..	70	..	79	3½ hr.
46	S. I.	5/29/34	L	36	32	..	85	43	39	43	50	
47	S. I.	6/ 5/34	L	36	32	7	77	55	50	53	47	4½ hr.
67	S. A.	7/ 2/34	T	12	50	..	92	62	47	46	52	
68	S. A.	7/10/34	T	12	..	7	83	..	93	..	71	½ hr.
69	S. A.	7/16/34	T	12	50	7	88	64	52	65	46	
73	G. R.	6/28/34	I	12	..	7	96	..	..	..	139	1½ hr.
74	G. R.	7/ 3/34	I	12	60	..	120	71	74	75	78	
75	G. R.	7/12/34	I	12	60	7	76	66	42	32	40	
96	C. W.	7/25/34	A	4	..	5½	...	..	..	..	..	8 hr.
97	C. W.	7/31/34	A	4	40	..	66	46	49	64	62	
98	C. W.	8/14/34	A	4	40	7	94	47	48	..	45	
C. Patients with No Convulsions												
1	R. C.	3/ ?/33	I	..	5	..	91	81	71	68	..	
2	R. C.	3/ ?/33	I	..	10	..	..	..	53	57	..	
3	S. T.	3/ ?/33	T	..	..	..	..	70	..	74	..	
4	A. I.	11/ ?/33	I	36	10	..	..	..	..	..	..	
5	A. I.	11/ ?/33	I	12	10	..	..	..	..	36	..	
6	A. I.	11/ ?/33	I	36	20	..	..	48	43	43	..	
7	A. I.	11/ ?/33	I	12	20	..	..	..	..	..	..	

* The experiments are listed in three groups to enhance comparisons: A, those with convulsions during the period of observation; B, those with convulsions during the following eight hours, and C, those without convulsions. The abbreviations in the diagnosis column are: I, idiopathic; T, trauma; A, alcoholism; L, syphilis; E, encephalitis; O, organic but not otherwise diagnosed; N, narcolepsy, and P, psychoneurosis. In the blood sugar columns, C indicates a convulsion.

TABLE 1.—*Summary of Observations in One Hundred and One Tests*—Continued*

Number of Experiment	Initials of Patient	Date	Diagnosis	Hours of Fast	Units of Insulin	Liters of Water	Blood Sugar Readings					Postobservation Convulsions
							Fasting	1st Hour	2d Hour	3d Hour	4th Hour	
			C. Patients with No Convulsions—Continued									
8	E. S.	12/ ?/33	I	36	10	..	85	..	57	61	..	
9	E. S.	1/ ?/34	I	36	25	..	73	45	55	52	..	
10	F. B.	12/ ?/33	I	36	10	..	87	..	57	53	..	
11	F. B.	1/ ?/34	I	36	20	..	81	63	49	43	..	
12	F. B.	1/ ?/34	I	36	25	..	78	43	..	37	..	
13	R. K.	1/ ?/34	E	36	10	..	80	..	61	67	..	
14	R. K.	1/ ?/34	E	36	25	..	121	45	47	46	..	
15	J. H.	1/ ?/34	I	36	20	..	84	49	57	62	..	
16	J. H.	1/ ?/34	I	36	..	..	..	56	45	43	..	
17	J. J.	1/ ?/34	I	36	20	..	62	..	51	47	..	
22	M. A.	4/11/34	L	36	..	4	..	..	..	..	..	
23	I. F.	4/11/34	T	86	..	4	..	..	..	..	..	
24	I. F.	4/ ?/34	T	86	25	4	91	63	71	..	..	
25	A. C.	4/12/34	I	36	25	7	79	52	52	55	..	
26	E. C.	4/12/34	T	36	..	4	..	..	..	..	..	
27	E. C.	4/24/34	T	36	25	7	76	60	55	53	..	
28	E. C.	5/16/34	T	36	25	..	80	65	65	80	..	
29	B. A.	2/19/34	I	36	25	7	82	42	41	42	..	
30	C. S.	4/26/34	L	12	30	7	71	41	50	44	..	
31	C. S.	5/ 8/34	L	36	30	7	73	50	50	49	..	
42	R. N.	5/14/34	I	36	35	7	81	52	44	50	..	
43	R. N.	5/31/34	I	36	35	..	50	49	..	28	44	
44	R. N.	6/ 5/34	I	36	..	7	54	..	..	..	65	
52	W. F.	5/28/34	I	36	..	6	105	..	..	..	..	
53	W. F.	6/ 8/34	I	36	35	..	175	45	51	47	56	
54	W. F.	6/21/34	I	36	35	7	76	48	50	54	59	
55	H. B.	5/31/34	O	36	..	7	100	..	..	..	81	
56	H. B.	6/ 4/34	O	36	37	..	133	72	70	75	92	
57	H. B.	6/13/34	O	36	37	7	150	82	73	75	60	
58	M. L.	5/21/34	N	36	..	5½	..	..	..	..	..	
59	M. L.	6/ 6/34	N	36	35	..	82	52	44	41	52	
60	M. L.	6/12/34	N	36	35	6	75	46	33	32	..	
61	E. M.	6/ 6/34	I	36	..	3	93	..	..	..	..	
62	E. M.	6/13/34	I	36	35	..	71	55	68	60	63	
63	E. M.	6/27/34	I	36	56	4	87	50	46	51	79	
64	S. B.	6/ 7/34	P	36	..	7	103	..	93	..	114	
65	F. P.	6/11/34	E	36	40	..	91	58	61	58	64	
66	F. P.	6/27/34	E	36	..	7	59	..	..	..	98	
70	L. W.	7/ 2/34	P	12	..	7	98	..	77	..	96	
71	L. W.	7/10/34	P	12	50	..	98	48	60	53	57	
72	L. W.	7/17/34	P	12	50	7	71	28	43	51	50	
76	S. C.	6/12/34	L	36	..	6	74	..	95	..	..	
77	S. C.	7/ 3/34	L	36	60	..	121	58	64	60	66	
78	S. C.	7/ 9/34	L	36	60	7	91	53	40	61	69	
79	A. K.	7/ 5/34	I	12	60	..	167	76	83	64	60	
80	A. K.	7/11/34	I	12	..	7	117	..	..	..	133	
81	A. K.	7/19/34	I	12	60	7	96	39	42	42	39	
86	A. I.	.....	I	12	..	7	107	..	..	..	103	
87	A. I.	7/18/34	I	12	40	..	87	73	70	76	58	
88	A. I.	7/24/34	I	12	40	7	80	64	65	67	69	
92	E. C.	7/24/34	E	36	40	7	84	54	50	46	48	
93	E. C.	7/30/34	E	0	..	7	109	..	..	..	..	
94	E. C.	8/ 6/34	E	12	40	..	78	51	50	57	57	
99	O. R.	7/30/34	I	36	50	..	104	13	80	77	74	
100	O. R.	8/ 6/34	I	12	..	4	83	..	72	..	..	
101	O. R.	8/14/34	I	12	50	7	89	47	62	..	56	

73 and 49 mg., respectively. These readings were taken twenty-five, fifty, twenty and twenty minutes, respectively, before the seizures. It may therefore be concluded that the convulsions which occurred with the administration of insulin plus water were not positively correlated with the decrease in the blood sugar content.

Superhydration.—Four convulsions were observed also during the thirty-one tests in which water alone was administered (series 3). The same number of convulsions occurred when water alone was administered as when water and insulin were given. This would indicate that the hypoglycemia produced by insulin played a relatively insignificant rôle, if any, in the precipitation of the epileptic attacks.

Convulsions which appeared after the four hour observation period might still be due to the effects of superhydration. This would apply to series 2 as well as to series 3, since in the former the hypoglycemia produced by insulin was terminated at the end of the tests by the administration of dextrose and orange juice by mouth. There were nine such attacks on the same day of the tests. Convulsions occurred in three instances (cases 48, 68 and 40) within thirty minutes after completion of the experiment. The other six convulsions (cases 36, 73, 18, 45, 47 and 96) followed in one, one and a half, two, three and a half, four and a half and eight hours, respectively. These seizures, with the possible exception of the last one, probably all occurred before the excess water was excreted and may all be attributed to the effect of superhydration. At least the number of seizures during this period was much greater than the estimated spontaneous incidence. The total number of convulsions, then, which occurred during superhydration (both series 2 and 3) was seventeen (eight during the test and nine during the subsequent eight hours), giving an incidence of seventeen of sixty-one trials, or 28 per cent. Seizures on subsequent days in the cases in which superhydration was produced were no more numerous than the spontaneous incidence of attacks.

Controls.—In the twenty-two patients on whom all three tests were conducted the results (table 2) on the whole confirmed those obtained in the larger group. No convulsions occurred when insulin was given, two when water alone was administered and three when insulin and water were used.

From the foregoing results it can be concluded that: (1) superhydration represents a potent factor in the facilitation of epileptic episodes and (2) superhydration, even when combined with the administration of insulin, is still the chief, if not the sole, factor in eliciting the convulsions.

CLINICAL IMPLICATION OF EXPERIMENTAL RESULTS

The major thesis of this study was to determine the effect of induced hypoglycemia on the convulsions of epileptic patients. Under the test conditions the incidence of convulsions was not increased. To what extent may one apply these experimental results to clinical considerations in epilepsy? Is one justified in saying that such fluctuations in the blood sugar in the direction of hypoglycemia as do or may occur spontaneously in epileptic patients are not responsible for seizures in these patients? Such a conclusion would be justified only if it could be demonstrated that the experimental procedure introduces no factors

which prevent seizures that would otherwise occur in a "spontaneous" hypoglycemia in the patient.

To exclude the possibility of the thirty-six hour period of fasting acting as a convulsion-inhibiting factor, one half of the patients were examined after a twelve hour period of fasting. The degree of hypoglycemia induced in both groups was approximately the same. Twice as many convulsions occurred after the thirty-six hour period of fasting as after the twelve hour period. In five experiments there was no preliminary period of fasting; no convulsions occurred in these cases.

The possibility of insulin giving rise to a side-reaction inimical to the development of seizures calls for comment. Only one symptom

TABLE 2.—*Results in Control Cases (Triple Series)*

	Experimental Conditions				Blood Sugar		Convulsions		
	Series I	Series II		Series III					
Numbers of Tests	Units of Insulin	Units of Insulin	Quarts of Water	Quarts of Water	Series I	Series II	Series I	Series II	Series III
26-28	25	25	7	4	65	53	..	..	..
32-34	25	25	5½	5	74	59	..	C	C
35-37	30	30	7	7	58	60	..	..	..
39-41	35	35	7	7	43	36	..	C*	..
42-44	35	35	7	7	28	44	..	..	..
45-27	32	32	7	7	39	47	..	..	..
48-50	40	40	5	7	52	61	..	C	C*
52-54	35	35	7	6	45	48	..	..	..
55-57	37	37	7	7	70	60	..	..	..
58-60	35	35	6	5½	41	32	..	..	..
61-63	35	35	4	3	55	46	..	..	..
76-78	60	60	7	6	58	40	..	..	..
73-75	60	60	7	7	71	32	..	..	..
67-69	50	50	7	7	46	46	..	..	C*
70-72	50	50	7	7	48	28	..	..	..
79-81	60	60	7	7	60	39	..	..	..
82-85	60	60	3	6	44	47	..	C	..
86-88	40	40	7	7	58	64	..	..	..
89-91	35	35	5	4	48	32	..	..	C
92-94	40	40	7	7	50	46	..	..	..
96-98	40	40	7	5½	46	45	..	..	..
99-101	50	50	7	4	73	47	..	..	..

* Convulsions occurring within one-half hour after the completion of the four hour period of observation.

observed may have had this influence, namely, a marked fall in temperature in thirteen of the fifteen patients receiving larger doses of insulin for whom the temperature was recorded. In one instance the temperature was 94 F. (95 F. rectally). Hypothermia produced by insulin is said to prevent convulsions in animals, whereas convulsions appear when normal temperature is maintained by artificial means.[4] This hypothermia is not peculiar to the hypoglycemia which occurs after the administration of insulin. Subnormal temperatures have been reported

4. Campbell, W. R., and Macleod, J. J. R.: Insulin, Medicine **3**:195 (Aug.) 1924. Voegtlin, C.: The Biological Standardization of Insulin: II. The Mortality and Glucose-Protective Test in Rats as a Method for the Bio-Assay of Insulin, Pub. Health Rep. **39**:1935, 1924.

with hypoglycemia in "spontaneous" hypoglycemia,[5] pituitary cachexia (Simmond's disease),[6] hypothyroidism,[7] hypo-adrenalism,[8] and extirpation of the liver.[9] Since hypothermia may be present in hypoglycemic states of varied origin, it is not an extraneous factor introduced by the experimental procedure.

Our patients were restricted in activity. Perhaps patients who are up and about, with more varied activity, would have convulsions more readily during the period of hypoglycemia. Of course, many of the seizures of epileptic patients occur during sleep and less frequently during muscular exertion.

Finally, ours was a selected group of epileptic patients. The basis of selection was: (1) age, (2) frequency of seizures and (3) type of epilepsy. The patients were all adults between 16 and 40 years of age. Those with relatively infrequent seizures were chosen in order to avoid complicating the statistics with too many spontaneously occurring convulsions. Both patients with symptomatic and patients with idiopathic epilepsy were included for purposes of comparison. We hold that both types are really "symptomatic"; in the former, the diagnosis is known, and in the latter it is unknown. The results revealed no difference in the response of either group to the experimental conditions. This selection of cases should not detract from the clinical application of the results.

From a consideration of the experimental conditions, it appears improbable that any foreign convulsion-inhibiting factors were introduced. One feels justified, therefore, in carrying the results of the tests to the clinical field. Hypoglycemia does not appear to play an important rôle in the precipitation of seizures in epileptic patients.

The results obtained on the production of superhydration represent a by-product of this study. A separate report will be made in this connection because of its bearing on dehydration therapy.

5. Griffith, J. P. C.: Hypoglycemia and the Convulsions of Early Life, J. A. M. A. **93**:1526 (Nov. 16) 1929.

6. Frazier, C. H.: Pituitary Cachexia, Arch. Neurol. & Psychiat. **21**:18 (Jan.) 1929. Calder, R. M.: Anterior Pituitary Insufficiency (Simmond's Disease), Bull. Johns Hopkins Hosp. **50**:87 (Feb.) 1932. Silver, S.: Simmond's Disease (Cachexia Hypophyseopriva): Report of a Case with Postmortem Observations and a Review of the Literature, Arch. Int. Med. **51**:175 (Feb.) 1933.

7. Osler, W., and McCrae, T.: The Principles and Practice of Medicine, ed. 9, New York, D. Appleton & Co., 1922, p. 867.

8. Hartman, F. A.; Brownell, K. A., and Crosby, A. A.: The Relation of Cortin to the Maintenance of Body Temperature, Am. J. Physiol. **98**:674 (Nov.) 1931. Reismann, D.: Diseases of the Adrenal Glands, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1926, vol. 3, p. 784.

9. Mann, F. C.: Studies in the Physiology of the Liver: I. Technic and General Effects of Removal, Am. J. M. Sc. **161**:37, 1921.

COMMENT

Since the present work was undertaken, a similar study has appeared in the literature. Baudouin, Azerad and Lewin [10] injected 10 units of insulin intravenously into seventeen epileptic patients. In all but three of nineteen tests a blood sugar level of 45 mg. per hundred cubic centimeters or less was attained. In three instances the low level was 27 mg. and in one 16 mg. There were no instances of coma or convulsions or their equivalent. The results are therefore similar to ours. The hypoglycemic levels obtained by these workers were much more transient than those which we secured because they administered the insulin intravenously.

Labbé and Escalier [11] also injected insulin intravenously in two epileptic subjects, recording very low blood sugar levels (once 10 mg.) without any symptoms. Pagniez [12] cited Jacchia and Fattovitch as having injected 28 units of insulin into an epileptic patient without hypoglycemia or convulsions resulting. Elias and Goldstein [13] in 1932 reported on the use of insulin in the focal diagnosis of cerebrospinal processes. The general statement is made that in epileptic persons insulin reproduced the seizures. Neither the number of cases nor the amount of insulin used is stated. Lennox and Cobb [14] gave insulin to an epileptic patient with severe diabetes, whose first convulsion came during an overdose of insulin, and obtained grand mal attacks in two of seven trials, during which the blood sugar level was reduced below 50 mg. per hundred cubic centimeters. In one of these tests the blood sugar level was depressed to 0.025 per cent, while the patient, though mentally confused, suffered no convulsion. At other times there were convulsions unrelated to injections of insulin, with the blood sugar at normal levels. All of these reports, except that of Elias and Goldstein, are in conformity with our conclusion that hypoglycemia induced by insulin in epileptic subjects does not precipitate convulsions.

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10. Baudouin, A.; Azerad, E., and Lewin, J.: Test of Hypoglycemia Produced by Insulin in Epileptics: Seventeen Cases, Compt. rend. Soc. de biol. **114:** 902, 1933.

11. Labbé, M., and Escalier, A.: Disturbance of the Carbohydrate Regulation in Epileptics, Médecine **13:**485 (July) 1932.

12. Pagniez, P.: Question of Existence of Epilepsy Due to Hypoglycemia, Presse méd. **41:**876 (May 31) 1933.

13. Elias, H., and Goldstein, J.: Insulin Shock and the Central Nervous System: Insulin in the Focal Diagnosis of Cerebral Pathology, Med. Klin. **28:**542 (April 15) 1932.

14. Lennox, W. G., and Cobb, S.: Epilepsy from the Standpoint of Physiology and Treatment, Baltimore, Williams & Wilkins Company, 1928.

Recent work by Hrubetz [15] has important bearing on this question. She found that insulin in dosages sufficient to reduce the blood sugar almost to "zero" (one-half to three-fourths unit per kilogram of body weight) did not produce convulsions in normal rats; our doses of insulin were of similar magnitude. However, "shock" dosage, from 1 to 4 units per kilogram of body weight, did produce convulsions in 2 per cent with the smaller doses and in 90 per cent with the larger doses.

The literature on related aspects of the problem must be given some attention. It has frequently been suggested that there is some disturbance of carbohydrate regulation in epilepsy. Much of the literature is covered in the monograph by Lennox and Cobb,[14] but a few papers have appeared since 1928. In general, the material does not convincingly demonstrate an etiologic relationship between hypoglycemia and seizures.

The problem in relation to cases of hyperinsulinism or hypoglycemia cannot be so summarily dismissed. Reference has been made to Harris' report on the frequency of convulsions in patients with hyperinsulinism. The same author [16] stated that hypoglycemia probably occurs as frequently as hyperglycemia. In that event one might expect numerous cases of hypoglycemic convulsions. Routine examination of epileptic patients does not bear this out. Possibly seizures are produced more readily by hypoglycemia in patients with hyperinsulinism than in normal or in epileptic adults. In the former the chronic depletion of blood sugar stores may result in an increased nervous irritability, so that convulsions appear at a certain still lower degree of hypoglycemia. Without this predisposing factor relatively acute hypoglycemia, as in our experiments, might not induce convulsions. From our point of view it suffices to show that in epileptic patients insulin in large doses does not precipitate seizures.

Considerations of the type entertained in this paper will undoubtedly obtain greater elucidation when (1) the mechanism of convulsions produced by insulin is known; (2) the instances of very low blood sugar level without symptoms are explained, and (3) the exact relationship between a low blood sugar level and the nutrition of the brain is better understood.

CONCLUSIONS

Insulin administered subcutaneously in doses of from 10 to 60 units to forty epileptic patients was not accompanied by convulsions in a single instance.

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15. Hrubetz, M. D.: Assay of Insulin and Blood Sugar Level, Am. J. Physiol. **107**:284 (Feb.) 1934.

16. Harris, S.: Hyperinsulinism, a Definite Disease Entity: Etiology, Pathology, Symptoms, Diagnosis, Prognosis and Treatment of Spontaneous Insulinogenic Hypoglycemia, J. A. M. A. **101**:1958 (Dec. 16) 1934.

Superhydration produced by the intake of 7 quarts of water at the rate of 1 quart every thirty minutes plus injection of insulin was accompanied by four convulsions in the thirty epileptic patients tested. The convulsions did not coincide with the lowest blood sugar concentrations. Further, the same number of convulsions resulted in thirty-one epileptic patients in whom superhydration alone was produced.

Spontaneous hypoglycemia is probably not a prevalent factor in the precipitation of seizures in epileptic patients.

Convulsions occurred in one fourth of the patients receiving large quantities of water.

INFLUENCE OF EMOTIONS ON DEXTROSE TOLERANCE

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The study of emotional reactions and their relation to physiologic functions is not yet far advanced. To speak merely of emotions and the associated bodily symptoms is much too general. One must study the various emotions separately and in this way become able to understand the more complex emotional reactions in which a number of emotions are present at the same time. There are many groupings of emotions which frequently lead to undesirable simplifications, as, for example, the attempt to consider fear merely a secondary elaboration of anxiety or to group emotions around the two antagonists, pleasure and non-pleasure. It is best to single out the most outstanding emotions which one observes under normal as well as pathologic conditions and to study them systematically. Situations must be created which have definite experimental value and which can be repeated. It is true that one cannot set up quite fully controlled conditions, as the personality involved is never the same at two different times. This is true, however, of many medical investigations, and many wide variations which are considered normal in physiology could no doubt be explained by psychobiologic variations.

The study of most segregated functions without the inclusion of the personality setting, however carefully and elaborately carried out, can never offer scientifically adequate results. Somatic functions are psychobiologically integrated, and consequently psychobiologic functions can express themselves in variations of somatic functions. Many highly integrated psychobiologic functions affect the physiologic functions in a definite way. This fact, however, does not mean that the production of these physiologic functions will produce a corresponding psychobiologic function. The hypothesis that such is the case, founded on a parallelistic mind-body concept, is responsible for the conclusion that because certain emotions like fear produced increased secretion of epinephrine, fear is produced by an increased secretion of that substance. Although they have attempted to do so, Marañon and others have not offered convincing evidence that the injection of epinephrine produces fear. It does produce a sensation of palpitation and associated reactions, and some personalities may react to these phenomena with slight anxiety.

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Others do not show these secondary emotional reactions to such sensations. Investigations of personality, therefore, must be based on the two fundamental concepts of the psychobiologic unit and individuality, viz., the study of the individual personality together with its reaction to the present (experimental and general) situation. One must investigate not only constitutional tendencies and their rôle in the experiment but also the person's past experiences, attempting to evaluate the extent to which latent emotional reactions associated with specific life experiences may be stimulated. One must consider further physiologic and psychobiologic phases of the individual person. An understanding of psychobiologic theories and methods of investigation is therefore essential for research in the field of the human personality.

Experimental investigations of personality disorders, i. e., psychiatric investigations in the broadest sense, necessarily involve the consideration of many relations and interrelations. One must consider the illness as an entity as well as the special phase of the illness which the patient may be undergoing at the time of the experiment and his reaction to the experiment both during the illness and when he is in normal health. The experiment, therefore, should be repeated during various phases of the illness and after recovery. It is not possible with present knowledge to test immediately the more fundamental features of such an illness. One must gain first an understanding of all the possible emotions which can enter into the experiment, even though they may be of incidental importance so far as the fundamental factors of the illness itself are concerned. Judging from the extensive literature, the necessity of distinguishing between essential and incidental features has usually been overlooked. The mere accumulation of data, especially without repetition of tests on the same patient and under varying conditions, cannot be interpreted. Investigations of physiologic functions in personality disorders have frequently, therefore, given varying and even contradictory results.

In the study of somatic findings in personality disorders—psychoses and neuroses—little attention has been paid to transient emotional reactions. It is unfortunate that many workers who have been especially interested in the somatic involvement have been guided by a concept of the pathologic entity with which they were concerned, disregarding the individual personality setting and the various phases of the illness. In many cases the various phases are due entirely to secondary or even incidental factors, e. g., transient emotional reactions. In other instances the occurrence of different phases may be of fundamental importance. In an agitated depression, for example, one may observe sadness, irritability and even anger, anxiety, constant tension, fear or terror. If one follows the whole course of the illness, one will observe that some of

these emotions subside earlier than others. In certain phases of the illness fear may dominate the picture; in other phases one observes merely anxiety and restlessness; at still other times, sadness is the leading emotion. The somatic findings may change accordingly.

CLINICAL INVESTIGATIONS

The foregoing remarks present the foundation on which these investigations in the field of sugar content of the blood and dextrose tolerance were carried out.

The variation of these somatic findings was studied in various normal persons over periods of from months to a year or more, under the varying conditions of daily life, as well as in patients who showed marked emotional reactions. Each personality was studied carefully; the setting at the time of the test and the test situation were analyzed, and continuous observations made during the test were supplemented also by the person's subjective observations. No tests were made just before or just after menstruation. During the test period the use of sedatives and nicotine was not permitted. Gross variations in diet were avoided. Whenever possible, an accurate chart of sleep, temperature, weight and intestinal elimination was obtained for a period of weeks or months. The usual amount of dextrose given was 1.25 Gm. per kilogram of body weight. Blood from a capillary was obtained in all the tests, and the sugar content was determined by the micromethod of Folin. Tests were made once a week and, in cases of prolonged observations, once a month, and according to the development of the emotional reactions. At no time was the interval between tests less than two days. Throughout the paper the curves for dextrose tolerance are shown as a series of five observations. These represent in each instance the sugar content in milligrams per hundred cubic centimeters of blood determined at the following times: during fasting and one-half, one, two and three hours after ingestion of dextrose. The emotion which influenced the test is indicated parenthetically at the end of each curve.

The investigations on anxiety, tension and fear are given first because these emotions are frequently found as incidental reactions in elated and depressed moods. The significance of the somatic findings associated with these emotions must be determined in order to understand the total picture. In studying the individual specific emotional reactions, attention was paid to the ease with which specific emotions occur, their intensity and the extent to which they persist. Whenever possible, I tried to make a test later, at a time when the person felt at ease. The curve obtained in that test indicates the individual base line.

1. *Anxiety.*—This is a vague and contentless emotion which seems to be rather closely related to the vegetative level of personality. In mild degrees it is described as uneasiness. When the emotion is stronger it occurs in the form of definite and circumscribed attacks. Fear enters into it secondarily; e. g., the fear of dying may be present in an attack of anxiety. Anticipation, if vague, expresses itself in anxiety; if it is more marked, fear develops. Anxiety may occur as an isolated emotion or in the setting of other emotions, especially depression. One speaks of anxiety depressions when anxiety dominates the picture of a depression. The physiologic alterations produced by anxiety were an increase in the

sugar level of the blood during fasting and an increased rise of the curve for dextrose tolerance, followed by a rapid fall, the level reaching that observed during fasting in from one to two hours. The increase of the level for sugar during fasting and the rise of the curve seemed to depend on the acuteness and intensity of the emotion. Anxiety was frequently provoked by the first test because of uneasiness with regard to an unknown situation. Only by successive tests was one able to determine the significance of this factor.

CASE 1.—An isolated occurrence of anxiety offered itself for investigation when a 30 year old woman of pyknic habitus, on whom tests had always given remarkably uniform results, was informed half an hour before the test of a possible neglect in the treatment of her infant's cold. This cheerful and easy-going mother was overconscientious when her children's health was concerned. The following curves for dextrose tolerance were obtained:

98—124, 116, 112, 92 (ease)
103—165, 141, 137, 93 (mild anxiety)

(More illustrations of the influence of anxiety in persons in good health and of attacks of anxiety are found under the heading of tension.)

In mild attacks of anxiety a correspondingly more accentuated curve was found.

CASE 2.—A 26 year old man of athletic habitus had suffered from weekly attacks of anxiety for two years. He carried on a normal and active life but was aware of symptoms of anxiety whenever any mildly upsetting situation occurred. The first curve was obtained at the beginning of treatment; the second, six months later, when he felt well and at ease. The results of the tests were as follows:

102—178, 161, 92, 73 (anxiety)
90—113, 119, 116, 100 (ease)

Variations similar to the preceding illustrations were not obtained in every case of anxiety neurosis. Between attacks a patient with a record of this kind may feel perfectly at ease for days. Anxiety appears only in provoking situations.

CASE 3.—A 22 year old man of pyknic habitus had suffered from attacks of anxiety for two months. In this man, usually easy-going, there had developed an anxiety neurosis to an unpleasant situation at home and difficulties at work. He felt quite at ease while he was in the hospital and two curves for dextrose tolerance, obtained on March 13 and April 5, respectively, were alike; they are represented by the following curve:

85—140, 119, 88, 76 (ease)

The patient complained of no symptoms of anxiety after he spent three days in the hospital (he had been admitted on March 8) but reacted with anxiety and two circumscribed attacks after having been informed (May 1) of his impending discharge. At the time of the test he experienced considerable anxiety but had no circumscribed attack. The test gave the following results:

May 4: 81—169, 122, 109, 82 (anxiety)

The influence of more topical and more circumscribed anxiety reactions can frequently be observed in patients with depressions, especially if they occur in association with anxiety and in apprehensive persons who lack self-confidence.

CASE 4.—A quiet, conscientious 42 year old man of pyknic habitus had a tendency to moodiness and discouragement. In October he reacted to increased responsibility connected with his work with a depression which gradually increased in intensity. On admission to the hospital (January 29) he was restless, agitated and anxious, had marked difficulties in thinking and felt markedly ill at ease in the clinic. He appeared quiet after about a week, and the depressed mood was more frankly dominant. The results of the test were as follows:

February 8: 104—123, 130, 110, 75 (uneasiness in a depression)

A second test, on February 11, produced considerable anxiety because the patient believed that something serious must have been found to necessitate a repetition, and the following results were obtained:

February 11: 110—177, 177, 110, 90 (anxiety)

During March and April the patient's depression improved steadily, but mild features of anxiety still appeared when anything distressed him. When he was discharged in good health in May he impressed one as an anxious person. A test made after improvement had occurred gave the following results:

April 26: 99—158, 106, 102, 80 (slight anxiety)

2. *Tension.*—This emotion develops when a person is torn between a desire and a counter-desire, between contradictory strivings, or when he has the need to overcome certain obstacles. If strivings and obstacles increase to the same extent, tension increases. Tension decreases or disappears if the desire decreases (one then gives up) or if the counter-desire or obstacle diminishes (one succeeds). Tension is frequently the result of strivings and desires which the personality as a whole wishes to suppress and which threaten to dominate. Tension is therefore always closely related to fear. Whether tension is merely a less marked degree of anxiety or a definitely separate emotion is disputed. In this discussion it is essential that one should consider it a subacute or chronic mood of varying intensity which occurs in every one's life and which may play a dominant rôle in personality disorders. In states of tension a normal sugar level during fasting and a slightly elevated curve with delayed fall were observed.

CASE 5.—This case is reported in detail because it illustrates well the variations which curves for dextrose tolerance may undergo in daily life. A teacher, aged 30, athletically built, active and cheerful, was observed for two years, during periods of ease and of strain of work. He carried responsibility well and was ambitious and intensely interested in the success of his work. The following curve was obtained when he felt well rested from a summer vacation:

Nov. 23, 1931: 89—140, 136, 103, 99 (ease)

The next two curves were obtained during a period of tension due to work with insufficient recreation:

April 10, 1932: 94—156, 144, 126, 80 (tension)
April 24, 1932: 95—158, 159, 121, 80 (tension)

A cure obtained at the end of a year of strenuous teaching showed the effects of the persisting tension:

June 14, 1932: 90—152, 135, 127, 84 (tension)

After two months of mere perfunctory teaching at summer school followed by six weeks' vacation the curve was as follows:

Oct. 4, 1932: 83—104, 125, 109, 81 (ease)

After the patient had for four weeks tried to solve an unpleasant situation and been unwilling to give in, the following curve was obtained:

Jan. 3, 1933: 95—108, 150, 142, 70 (tension)

After the situation had passed and the patient felt more at ease, the curve was as follows:

March 9, 1933: 92—119, 136, 115, 77 (mild tension)

After increased strain at work he again felt tense. At times of tension, he showed little to outsiders, but he noticed the need to exert more effort to conceal irritability and some restlessness. The results of the tests were as follows:

April 28, 1933: 88—116, 133, 112, 110 (mild tension)

An interesting group of persons who showed tension and to some extent anxiety were five students in the medical school. They were selected according to their personality make-up and for the purpose of this study were divided into two groups—those of steady, even-tempered, and those of more intense, excitable, type.

CASE 6.—Student A., a 22 year old person of athletic habitus, placid and self-assured, had a tendency to procrastination in work. At the beginning of the school year he was slightly tense, being disturbed by some personal problems. The results of tests were as follows:

November 11: 95—155, 121, 120, 117 (tension)
December 17: 96—130, 112, 115, 102 (ease)

In March he felt somewhat uneasy, fearing that he might not succeed in finishing delayed required work; the following curve was obtained:

March 18: 89—145, 100, 83, 82 (mild uneasiness)

About the middle of May a period of tension and uneasiness started because of the impending examinations which were to begin on May 29, and the test gave the following results:

May 25: 93—145, 168, 123, 95 (tension)

Two days after examinations were completed the student had slept well but was waiting for the results (all the students in these groups were in good standing, and there was little likelihood of their failing). The curve was as follows:

June 6: 88—160, 152, 103, 89 (mild anxiety)

A week later he felt at ease and rested, but to me he still appeared somewhat anxious, and the test gave the following results:

June 14: 94—158, 121, 114, 102 (mild anxiety)

CASE 7.—Student B, a quiet man aged 22, of asthenic habitus was excitable and quite tense. To the first test he reacted with slight anxiety, his usual reaction to a new situation, the curve being:

October 17: 100—150, 150, 92, 80 (mild anxiety)

In December he worked hard, was more tense and felt "under push," and the test gave the following results:

December 22: 89—170, 179, 91, 70 (anxiety)

With the approach of examinations he noticed slight general fatigue. The curve was as follows:

April 6: 91—186, 187, 127, 108 (anxiety and tension)

To the impending examination he felt "excited," and the results of the test were:

May 18: 85—153, 194, 165, 127 (anxiety and tension)

When I saw him while I was giving examinations, he was flushed, his hands were perspiring freely, he experienced palpitation and felt "excited." Two days after the examination he still felt excited and looked flushed. The curve was as follows:

June 6: 94—200, 173, 101, 78 (anxiety)

A week later he was still slightly flushed and did not feel at ease yet, the test showing:

June 13: 96—171, 159, 82, 68 (mild anxiety)

These cases indicate clearly that the body takes a considerable time to return to its optimal balance after being subjected to the prolonged effect of a sufficiently intense emotion. Fatigue, which is the most frequent somatic complaint in states of tension, seems to yield well to physical recreation.

In states of prolonged tension of pathologic intensity symptoms of anxiety may be observed.

CASE 8.—The results of the following two tests on a 35 year old woman of asthenic habitus who had been seen occasionally over a period of years because of complaints of marked tension and occasional anxiety are rather characteristic. The second test, made when the patient felt under more strain and experienced more tension, gave the following results:

October 31: 90—149, 135, 120, 87 (mild tension)
December 27: 99—145, 168, 141, 91 (marked tension)

These studies have shown that tension, as a subacute and prolonged emotion, caused no appreciable change in the sugar level during fasting but caused a definitely delayed fall in the curve for dextrose tolerance, with or without a rise to a higher level than usual. According to the constitutional make-up, considerable individual differences occurred. The opportunity of observing the curves for dextrose tolerance when anxiety occurred in a setting of tension was afforded by the following case:

CASE 9.—As an illustration of the combined influence of both emotions, anxiety and tension, the case of a 24 year old woman of pyknic habitus is of interest. This

emotionally unstable woman had suffered four attacks of anxiety and increasing tension for two years. She was in the hospital from February 8 to April 24, and soon after her admission she felt at ease, being removed from environmental influences which had a large bearing on the illness. During her stay in the hospital, however, she reacted with anxiety to any new situation. The first test, which was made in the ward, did not upset her. It gave the following results:

February 17: 92—153, 150, 132, 92 (tension)

The second test caused the patient marked anxiety because she was the only one of her group who had been asked to go to the laboratory in another building. The curve was as follows:

February 23: 100—246, 145, 143, 100 (anxiety in a setting of tension)

All the subsequent tests were made in the same laboratory without causing anxiety. At the end of February the patient felt more at ease, and the results of the test were:

March 1: 89—136, 124, 116, 73 (mild tension)

In March, tension increased when discussion of her problems was undertaken with the purpose of finding constructive solutions, and the curve was as follows:

March 7: 97—156, 162, 133, 131 (marked tension)

The patient finally seemed to become more resigned to her home life and willing to adjust herself to whatever situations could not be changed, the test giving the following results:

April 5: 98—135, 146, 139, 102 (tension)

When the patient heard of her impending discharge tension increased, and on April 20, after she had been told of her husband's expected arrival two days later, mild anxiety reappeared. The patient felt unable to cope with the unpleasant situation at home. On April 22 she left the hospital and was willing to try to adjust herself, but she has since been unable to do so. She is unwilling to live with her "in-laws" and, on the other hand, unable to take the full responsibility of running her own house. The following curve was obtained when tension had increased:

April 21:—103—157, 172, 144, 135 (anxiety and tension)

It is clear that in case 9 an elevated level for sugar during fasting as well as a markedly increased rise in the curve for dextrose tolerance occurred when acute anxiety complicated the state of chronic tension.

3. *Fear.*—This emotion is more or less immediate and concrete, having a definite content. The threat lies before one, in the future. Threats of the past may cause fear because one is afraid of the recurrence of the threatening situations. The threat may be real or imaginary. The intensity of the emotion varies greatly and does not depend on whether its development is acute, subacute or chronic. In psychopathologic conditions, fear reactions are frequently observed as mere incidental emotions, as in daily life, or as important emotional reactions, either isolated or dominating a prolonged phase. In prolonged states of fear tension is the outstanding mood between the reactions of acute fear. In the present study the sugar content of the blood during fasting was found to be considerably elevated in states of acute fear, whereas it

was little raised in states of chronic fear. After administration of dextrose there were a marked rise and abrupt fall in the curve for sugar content of the blood, depending on the intensity of the emotion. A delayed fall was found to be associated with prolonged states of fear and panics or with acute fear occurring in a setting of marked tension.

CASE 10.—A 36 year old woman of asthenic habitus had suffered from phobias for three years. When she consulted me in the summer of 1931, she felt constantly uneasy and tense. The results of tests at that time and in 1933 corresponded to her fear and tension, being as follows:

July 23, 1931: 89—194, 183, 131, 83 (chronic fear and tension)
Nov. 3, 1933: 95—180, 180, 125, 107 (chronic fear and tension)

Under intensive treatment during eight months, starting in November 1933, phobias and fear subsided rapidly while tension persisted.

Dec. 11, 1933: 97—138, 149, 130, 115 (tension)
Feb. 5, 1934: 92—136, 144, 127, 123 (tension)

After having mentioned some "revolting" memories on May 25 the patient was acutely disturbed for the following few days; she felt more tense, uneasy and excitable but did not experience acute fear.

May 26, 1934: 98—175, 166, 126, 97 (anxiety and tension)

No other tests were made during the remainder of treatment, during which the patient lost the phobias and most of the tension. At a visit in April 1935, she felt well but stated that she experienced some fear when attempting to drive a car. Her most disturbing phobia had related to being in an automobile. She had never dared to learn to drive a car until April 1935. Three days after a test had been made which gave results similar to those usually found in a person at ease, the patient was advised to drive a car in front of the building before taking dextrose. She showed a slight reaction of fear. The curve was as follows:

April 7, 1935: 97—151, 132, 94 86 (ease)
April 10, 1935: 110—165, 153, 86, 106 (acute mild fear)

Isolated reactions of fear in patients who are greatly disturbed emotionally may produce far reaching effects. In such cases it is frequently difficult to single out the various emotions and to determine their influence. Fear may reach a maximal degree (panic) for a brief period, while at other times anxiety and tension may predominate.

CASE 11.—A man athletically built, aged 47, was admitted to the hospital on November 30 in a recurrent depression which had lasted for a year. In the previous two weeks he had been greatly agitated; he feared that he might have syphilis or be declared insane. At this phase of the depression anxiety and fear dominated. On December 2 the patient, misunderstanding a remark he had overheard, became acutely afraid that he might be transferred to another institution on the following day, and the test gave the following results:

December 3: 111—195, 269, 247, 88 (acute fear and anxiety)

The fear increased and reached the degree of panic with paranoid features within a few days. The patient continued to eat well. Another test gave results as follows:

December 10: 114—280, 332, 161, 67 (acute panic)

The physician succeeded in allaying this acute fear, and the patient began to feel less afraid, the curve changing to:

December 13: 102—180, 153, 87, 87 (fear)

Six more tests which were made during the period of five months gave similar results, variations depending on the emotions at the time of the test. When the patient felt more depressed, hypochondriacal concern with anxiety was associated with a sugar content varying from 100 to 115 mg. during fasting and with a rise of the curve to from 223 to 252. When he was not acutely disturbed the curves were those usually found in association with tension.

Panic is a maximal state of fear which results from prolonged tension and insecurity. When the fear was not acute at the time of the test the sugar content during fasting was not altered in any characteristic way. The curves for dextrose tolerance showed a sharp rise, reaching, according to the intensity of the fear and to constitutional somatic factors, from 180 to 300. The fall of the curves was greatly delayed, occasionally to a degree that suggested a diabetic curve (cases 22 and 23).

CASE 12.—A 46 year old woman of pyknic habitus had been depressed for two months and had been admitted to the hospital on October 24 because she had been in a state of panic associated with paranoid features for five days. During this phase, which persisted for about a week after the patient entered the hospital, she was afraid of medical interference. Later the panic decreased rapidly. The curves were as follows:

October 31: 104—220, 217, 178, 131 (panic with acute fear)
November 11: 101—187, 187, 127, 85 (panic)

After discussing a disturbing problem relating to masturbation (November 12) fear and panic increased again and ideas of reference reappeared for two weeks. The results of the test were:

November 20: 107—208, 237, 186, 71 (marked fear and panic)

In December and January the patient improved steadily. She was deeply depressed; slight fear and anxiety were always provoked by tests but were absent otherwise. The curve was as follows:

December 28: 102—168, 171, 134, 73 (fear and tension)

Tests which were made during the remainder of the patient's stay in the hospital, which was terminated by recovery in August, are not discussed here because the results were influenced by anger and resentment to the test or by transient anxiety about her condition.

4. *Depressed Mood.*—It is difficult to study the emotions of pure sadness and depression because topical concerns usually produce incidental emotions, such as anxiety and apprehension, which influence the findings. Pure depressed mood did not seem to influence the sugar content of the blood during fasting or the dextrose tolerance. This was studied in cyclothymic as well as in pathologically depressed patients.

CASE 13.—A 28 year old man of pyknic habitus was observed for one and a half years. He had unaccountable periods of mild depression and of elation not

caused by any special situations and never interfering with his work, although usually noticed by his co-workers. On Nov. 16, 1933, he was somewhat tense but not depressed, being disturbed by some minor physical complaints. The test showed:

98—140, 135, 118, 103 (mild tension)

The following curves were obtained when he was feeling "blue" or definitely elated:

March 3: 95—145, 125, 106, 97 (slight depression)
March 31: 100—130, 122, 100, 102 (mild elation)
April 26: 100—132, 152, 100, 107 ("low spirits")

In cases of depressive psychoses similar observations were occasionally made. The curves in case 14, as well as isolated curves in other cases, confirm the fact that pure depressed and elated moods do not affect the dextrose tolerance.

CASE 14.—A 34 year old woman of pyknic habitus had suffered from a depression for eight months. In the beginning of her stay in the hospital (she was admitted on March 27) slight anxiety was present. The curve was:

April 2: 88—160, 143, 79, 95 (mild anxiety)

She improved rapidly, and topical concerns disturbed her less, but she still felt depressed in the morning, the test showing:

May 1: 87—142, 115, 89, 78 (depression)

When urged to see friends while in the hospital this sensitive person reacted with mild anxiety, and the curve was:

May 22: 82—157, 150, 106, 75 (mild anxiety)

Depressions are usually accompanied by impure affects, the nature of which depends on the dynamic factors involved and on the constitutional make-up. The most frequent impure affects found are anxiety and tension.

CASE 15.—A 42 year old man of asthenic habitus had a second attack of depression in September 1934, with anxiety and apprehension. On admission to the hospital, on December 1, he was tense, ill at ease and depressed. The results of the test were:

December 3: 93—160, 152, 139, 101 (tension in depressive setting)

He soon felt more at ease, although he was still depressed. In January he strained his foot, and this slightly worried him for a few days. The curve at that time was as follows:

January 5: 103—167, 142, 103, 77 (transient anxiety in depressive setting)

At the end of January, as a decrease of the depression occurred, discussions relating to personality were started. The patient became again aware of his difficulties; tension returned, and anxiety was present for a few days, the test showing:

February 5: 118—190, 165, 152, 130 (acute anxiety in setting of tension)

In March there was a considerable improvement in tension. The patient felt only slightly depressed in the morning and at these times was anxious about his future. The curve was as follows:

March 19: 98—167, 156, 96, 109 (mild anxiety)

At his discharge, on March 30, he was his usual self, a cheerful but slightly tense man, and the test gave the following results:

March 28: 100—142, 142, 112, 106 (mild tension)

Marked anxiety is frequently observed in cases of depression occurring in emotionally unstable psychopathic persons.

CASE 16.—A 50 year old woman of athletic habitus became depressed in October 1930; she was given to constant self-accusations about past sexual misdemeanors and outbursts of marked agitation and screaming. When admitted to the hospital on April 11, she was agitated and anxious; she talked a great deal about her sexual life but tried to control herself otherwise. The test gave the following results:

April 16: 106—187, 201, 128, 100 (anxiety)

In the following two weeks the patient became more quiet, although anxiety persisted and her deep depression was more obvious. The curve was as follows:

May 8: 106—163, 178, 125, 91 (anxiety)

As the patient did not adjust herself in the ward, she was transferred to a ward for disturbed patients on May 22. She reacted with marked outbursts of anxiety and screaming and with considerable resentment. This acute emotional reaction subsided after a few days, but she remained agitated, showing marked anxiety and occasional outbursts of screaming until she was again transferred, on June 27. The results of tests were as follows:

May 24: 108—200, 231, 160, 93 (acute anxiety and resentment)
June 7: 110—196, 221, 202, 121 (acute anxiety and marked tension)

Resentment: This mood, which is closely related to anger and hate, is a frequent reaction to life situations and is especially marked in some patients with depressions. When a depressed patient has an aversion to accepting his illness and medical help the test situation may provoke acute resentment. Tension caused by fretting and inability to adjust accompanies prolonged resentment. In patients suffering from such a mood the sugar content of the blood during fasting was often markedly elevated. More characteristic, however, were the acute rise and rapid fall in the curve for dextrose tolerance. The delayed fall in the curve, occasionally observed, may have been related to the more chronic mood of resentment and the accompanying tension.

CASE 17.—Resentment of medical interference and the acute provocation by the test are illustrated by the reaction of a 42 year old man of asthenic habitus who was in his second attack of depression. Although when less depressed, in the afternoon, the patient was willing to accept medical treatment and impending tests, he resented the procedures violently when deeply depressed, in the morning. The first test provoked the most acute reaction, giving the following results:

November 1: 98—290, 261, 143, 75 (resentment to test)

Subsequent tests caused less marked reactions (a rise to from 222 to 246). Even after the depression had largely disappeared, the patient still showed resentment in the morning. He was discharged on May 28 and recovered fully a few weeks later. In April a test gave the following results:

April 16: 93—191, 219, 142, 108 (resentment and tension)

5. *Elation.*—The emotion of pure elation did not seem to influence definitely the curve for dextrose tolerance, although the sugar content during fasting seemed to be somewhat elevated. This was true of varying degrees of intensity of normal and pathologic elation. When elation is complicated by impure affects, such as anger, resentment, anxiety or tension, it may be associated with considerable change in the curve for dextrose tolerance, as would be expected from the curves obtained during anxiety and tension. The cyclothymic patient (case 13) presented an example of mild elation. Hypomanic patients also had normal curves (case 18). Even in cases of marked manic excitements, my findings were normal if the patient's cooperation could be gained and if excessive physical overactivity did not interfere.

Case 18.—A 27 year old woman of pyknic habitus was observed during her third attack of manic excitement. In April she was elated, overtalkative, highly distractible, overactive and pleasant; she showed some flight of ideas but no irritability or anger. Tests gave the following results:

April 9: 100—146, 115, 109, 111 (marked elation)
April 19: 94—146, 136, 92, 87 (less elation)
May 23: 87—134, 120, 94, 88 (hypomania)

Anger: This is an acute emotion, and in this study it was accompanied by a more or less marked increase in the sugar content of the blood during fasting and a sharp rise in the first half hour after ingestion of dextrose, followed by a rapid fall.

Case 19.—A 20 year old girl of athletic habitus had exhibited a marked manic excitement for two months; she was overactive, danced, laughed, was overtalkative, showed marked distractibility and was easily angered. She cooperated well during both tests, but on the morning of the second test had been angered by an occurrence in the ward. The results of the tests were as follows:

March 28: 92—145, 105, 100, 95 (marked elation)
April 19: 99—158, 104, 81, 100 (slight anger in elation)

Anxiety may occasionally be an important factor in a hypomanic reaction. To the group of patients with moods of anxiety belong those in whom an underlying depression can be recognized.

Case 20.—A 55 year old man of pyknic habitus had been hypomanic for three months. In the clinic he was self-assertive, elated and overtalkative, but one was able to recognize underneath this persistent hypomanic picture considerable anxiety caused by concern about the threatened loss of his position. On admission to the hospital on December 9 he reacted therefore with anxiety, the curve being as follows:

December 13: 89—209, 239, 132, 65 (anxiety in elation)

He improved steadily and was discharged (January 25) in a mild hypomanic condition, not quite reassured with regard to his position. Tests gave the following results:

January 9: 91—169, 202, 133, 116 (less marked anxiety in elation)
January 21: 95—154, 159, 102, 114 (slight anxiety in elation)

Manic excitements with marked tension are infrequent. They are usually diagnosed as mixed manic-depressive illness. In patients with such disorders the findings correspond with those exhibited by patients with marked tension. The following curve was obtained for a patient with elation associated with tension:

100—132, 180, 153, 120

Body Build.—A consideration of the body build in all the cases in this series did not lead to any definite correlations.[1] In some cases (cases 21 and 22) the constitutional factor may have influenced the curves for dextrose tolerance.

CASE 21.—A 58 year old man of asthenic habitus had always been a tense person who reacted readily to any strain with increased tension and marked indigestion (hyperacidity). The curves are of a type frequently observed in tense persons who lead an active life. He was admitted to the hospital on January 19, suffering from a recurrent mild depression which had lasted three months and was characterized by depressed mood, tension and hypochondriacal anxiety with regard to gastric distress. The patient improved steadily. The depression and gastric disturbances disappeared early in March, and the patient was his usual self when he left on March 14—a tense, somewhat hypochondriacal person who had a tendency to anticipate difficulties, to take responsibility too seriously and to neglect the necessary recreations. The results of the test were as follows:

February 16: 97—241, 163, 144, 69 (anxiety and tension in a setting of depression)
March 10: 101—165, 151, 148, 79 (tension with slight anxiety)

On December 28 the patient was readmitted, suffering from a similar depression of six weeks' duration. The depression disappeared in the middle of January, and the patient left the hospital on February 10. Tests gave the following results:

December 29: 106—215, 220, 68, 72 (anxiety in depression)
February 4: 98—179, 222, 129, 82 (tension)

When he consulted me later, the patient stated that he had maintained a healthier routine and had felt in better health than he had for years. The curves were as follows:

March 17: 92—189, 203, 110, 62 (anxious and intense state)
June 1: 91—155, 205, 101, 92 (anxious and intense state)

In some persons who had reacted with prolonged anticipation and tension, a diabetic curve was found.

CASE 22.—A 42 year old banker, of athletic habitus, had suffered from considerable tension for several years. A few months before he consulted me he began to notice slight tremor of the fingers, and there developed marked anticipation to signing checks which was part of his routine at the office. When he was seen on November 1 he was tense and flushed and had marked tremor of the fingers. Two weeks' treatment by hypnosis and reassurance caused marked

1. Hirsch, O.: Blutzuckerbelastungsproben zur blutchemischen Fundierung der Körperbautypen, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:710, 1932.

improvement, and the patient was able to return to work. During the spring of 1935 the symptoms disappeared, but tension remained. Tests gave the following results:

Nov. 3, 1934: 90—162, 231, 240, 197 (marked tension and anticipation)
Nov. 10, 1934: 99—235, 232, 244, 209 (marked tension and anticipation)
Nov. 22, 1935: 71— 87, 135, 156, 132 (tension)

Similar curves are exhibited by patients with prolonged fear. They may be associated with panic reactions (case 12) but do not reach the same height as those of constitutionally predisposed persons. All the patients who showed high curves excreted a considerable amount of sugar in the urine.

CASE 23.—A 31 year old man, of athletic-pyknic habitus, was admitted to the hospital on March 21, in a state of marked panic which had lasted three weeks. Although paranoid delusions persisted, fear disappeared at the end of April and puzzlement and depressed mood were prevalent. Tests gave the following results:

March 22: 110—165, 175, 156, 153 (panic)
April 12: 104—147, 174, 171, 130 (panic)
May 10: 98—151, 151, 118, 123, 113 (uneasiness)

In these cases diabetes had been excluded by clinical study and, in case 22, by control examinations over a period of years. In many of the cases, including case 22, in which there was a delayed fall in the curve, intravenous tests for dextrose tolerance were made. They showed a slight delay in return to the level observed during fasting but the results were quite different from those of intravenous tests for dextrose tolerance obtained even in mild cases of diabetes.[2] My observations, however, were not extensive enough to indicate to what extent emotions influence curves obtained after intravenous administration of dextrose.

EXPERIMENTAL INVESTIGATIONS

A personality reaction to a given situation can be utilized as a clinical experiment. In illness, nature offers additional experiments which can be utilized for confirmation of observations made in daily life. The task is to establish methods of observation and investigation which do justice to the peculiarities of personality functions and allow control of carefully selected and organized material. At the Phipps Psychiatric Clinic the working principle is as follows:

. . . the facts must be accepted in the form in which they are most distinctive and also most controllable, either by corroboration in reobservation or, whenever possible, by test, i. e., by performances obtainable at any time. The latter desider-

2. Moracchini, R., and Barone, V. G.: Sulle curve glicemiche, consecutive a somministrazione perorale, endovenosa, ipodermica e rettale, di glucosio, Clin. med. ital. **63**:399, 1932.

atum must be recognized as only partly attainable. Man is an entity that does not respond in any invariable manner.[3]

In order to establish experimental conditions for verification of the clinical observations, I looked for provoking situations in the patient's life which could be repeated under controlled circumstances. This was possible in relatively few cases. Sudden attacks of anxiety, for instance, can rarely be produced under experimental conditions. More suitable are patients with phobias and compulsions, who when forced to carry out the feared act react with marked anxiety, although rarely with attacks of anxiety. The results of an experiment of this type are demonstrated by the last curve in case 10. Frequently these patients are under a more or less marked and continuous tension on which the acute anxiety is superimposed. These two factors need to be distinguished in the interpretation of the curve for dextrose tolerance.

CASE 24.—A 26 year old woman of asthenic habitus had suffered from compulsions of washing of hands and of cleanliness for three years. Owing to their marked increase she was admitted to the hospital on January 15. For ten days nobody interfered with the carrying out of her compulsive activities and she seemed to feel at ease. The first two tests, made on January 18 and 22, respectively, gave practically identical results. The results of the second test were as follows:

January 22: 86—153, 125, 98, 70 (slight anxiety)

On January 25, the sugar content of the blood during fasting was 81 mg. per hundred cubic centimeters. The patient was then ordered to touch objects which were disgusting to her and to prepare a lemonade without having an opportunity for cleaning herself satisfactorily. This involved little physical activity. The whole procedure lasted fifteen minutes. The pulse rate increased from 72 to 94. The sugar content of the blood increased to 86 mg., the results of the test being as follows:

January 25: 86—165, 192, 171, 95 (anxiety)

In other cases of compulsive activities no anxiety was produced by suppression because the compulsions had lost their significance. To this group belonged a case of senile depression associated with compulsive washing of hands.

CASE 25.—A 20 year old man of athletic habitus had suffered from many compulsions for six years. When they were suppressed in the clinic he became irritable, but no actual tension or anxiety resulted, and his pulse rate remained at a low level. The first test was made after a prolonged period without interference; the second was made after the patient had been exposed to upsetting activities, and the third, after three weeks' suppression of all his compulsions. The results were as follows:

April 15: 82—131, 98, 79, 74 (ease)
April 18: 94—126, 89, 84, 55 (ease)
May 5: 98—123, 91, 101, 91 (ease)

3. Meyer, A.: Preparation for Psychiatry, Arch. Neurol. & Psychiat. **30**:1111 (Nov.) 1933.

Stutterers are another group of patients in whom experimental anxiety can be produced. When uneasiness interferes with free talk stuttering occurs. There are always specific situations to which the person is more sensitive and in which, if he is required to speak, anxiety develops.

Case 26.—Tests made on a 26 year old woman of pyknic habitus when she felt at her best, although showing considerable tension, gave the following curve:

83—149, 156, 122, 77 (tension)

Definite anxiety was produced by having the patient talk into a telephone. The results were: during fasting, the sugar content of the blood was 91 mg. per hundred cubic centimeters; immediately after a five minute telephone conversation with increased stuttering, five minutes after the first test, the sugar content was 102 mg., the curve being as follows:

102—163, 171, 123, 98 (anxiety)

Experiments with animals are necessary amplifications and corroborations, but they can never take the place of the experiment on human beings in psychobiologic research. The human personality alone is able to give a subjective description of various moods and to indicate these moods objectively in well differentiated modes of behavior. The studies on sugar content of the blood which have been made on animals should, therefore, be checked on human beings in order to enable one to determine the different emotions which enter into the experiment. There is still a deplorable lack of methodical approach to the study of animal individuality, and most investigators apparently pay little attention to an animal psychology, the observations on which could be compared with a study of human personality.

It is difficult to produce more or less pure emotional reactions in an animal. Fear, for instance, is usually accompanied by anger or motor excitement. What Pavlov described under the entirely misleading term of neurosis corresponds to what one calls tension in human beings. The dog does not know to which of two stimuli he should respond because they come too close together. He becomes increasingly uneasy and tense and presents all the clinical symptoms which one is accustomed to observe in a person with pathologic tension. No attempt has been made to investigate the factors in the dog's make-up which cause him to exhibit one or the other type of Pavlov's "neurosis" under the same experimental conditions. As in patients, such tension takes a long time to disappear and can be relieved only by months of rest, i. e., by removal and avoidance of the stimuli which cause the tension. In unpublished experiments with dogs Dr. Roger B. Loucks and I were able to obtain a curve for dextrose tolerance revealing changes which corresponded to those observed in the case of patients with tension.

COMMENT

In studying emotions it is essential that one consider the type, depth, acuteness and duration of the emotion and the constitutional setting. In the present work, emotional reactions as they occur in daily life and in association with personality disorders have been singled out—pure elation and depression, anxiety, tension, fear, anger and resentment. In pure elated or depressed moods, with the exception of an occasional elevated sugar content during fasting no characteristic changes in the curves for dextrose tolerance were observed. On the other hand, in cases of other emotions considerable changes were noted in the curves for sugar. It is at present not possible to state whether some of the curves described were associated with the type of the emotion or whether they were due to difference in acuteness and duration. The latter might be true for the differences between anxiety, fear and tension. (The last curve in case 10 might occur in anxiety as well as in fear.) Although in elated and depressed moods different degrees of acuteness and intensity did not affect the curves, in general, the more acute an emotion the more marked were the changes in the curves for sugar. In the acute emotions the curves showed a steep rise and, usually, a rapid fall. In the emotions such as fear, anxiety, resentment and anger, the rise in the curve for dextrose tolerance was more marked than usual. Roughly, the more intense the emotion the higher the apex of the curve for sugar tended to be. The sugar content during fasting was increased more by acute strong emotions than by strong emotions of long duration.

With regard to the constitutional setting, some persons have a marked ability to react emotionally and often with considerable intensity. There is in some persons greater readiness of body response than in others. In other persons only one or the other of these factors may be active, or there may even be a definite lack of emotional and somatic responsiveness. Moreover, one has to guard against being too much guided by a person's complaints and subjective description. Some have an ease of display which does not correspond to the same depth of emotions as that displayed by like reactions in the average person. Hypochondriasis, for instance, in an anxious person with ease of display of emotions may impress the observer as marked anxiety. Other persons have a diminished ability to display emotion or try to conceal their emotions or to dissimulate. In some psychoses the display of affect may persist although the emotions have lost their depth and become shallow. This is frequently observed when personality changes associated with arteriosclerosis develop in the course of a depression in older persons. In hypochondriacal and anxious persons the feature of

agitation may persist with little change, even after the depressive illness has improved greatly. These two types of depression emphasize the need to study carefully the individual emotion and the patient's somatic expression of emotions before trying to utilize laboratory findings, especially the curve for dextrose tolerance, for prognostication or evaluation of recovery. The effect of depression, as in illness, for instance, on the carbohydrate metabolism can be studied only after one has gained an understanding of the many emotions which play a rôle and of the person's individual somatic response. In content psychoses (especially schizophrenic and catathymic reactions) it is still more difficult to evaluate emotional factors.

It is not possible in a brief space to enter into a full discussion of all the mechanisms which may be concerned in the regulation of the sugar level of the blood. I omit all discussion of the possible action of the central nervous system and limit myself to a few remarks which are offered as mere suggestions. The mechanisms involved need to be determined in the future.

The observations that the sugar content of the blood during fasting showed a definite tendency to be more elevated in cases of acute than in those of chronic emotions might be interpreted as indicating a response to the discharge of epinephrine in the cases of acute emotions. This would be in accord with Cannon's work.

With regard to the tests for dextrose tolerance, the curve for sugar throughout its course is determined by the factors of rapidity of absorption and of rate of removal of sugar from the blood. It is probably only in the first portion of the curve that the sugar level is largely determined by the rate of absorption. Although no gastro-intestinal investigations were carried out during the present study, it seems likely that the high early peaks in the sugar content of the blood, observed especially in cases of acute anxiety and fear, indicate unusually rapid absorption of the dextrose. No consistent and clear evidence of delay of absorption can be found, although such a delay is suggested by some of the curves. The rapid descent of the sugar level following such peaks suggests that the insulin mechanism is functioning efficiently. On the other hand, in the less acute state of tension in which the sugar content of the blood fails to return to normal in the usual time or even continues at levels suggestive of diabetes one wonders whether an otherwise normal insulin mechanism may not be counteracted by an overactive sympathetico-adrenal apparatus, as suggested by the results of physiologic experiments.[4]

4. Bridge, E. M., and Noltie, H. R.: The Action of Adrenaline on the Respiratory Quotient, J. Physiol. **85**:334, 1935.

SUMMARY

In investigating the somatic findings of psychobiologic reactions in psychopathologic conditions, as well as in ordinary life, one needs to evaluate critically the emotional factors involved. Attention should be paid to the type, depth, acuteness and duration of the emotions, the constitutional tendencies of emotional responsiveness and display and of body response. From such a point of view, emotional reactions have been singled out and their influence on the sugar content of the blood and on dextrose tolerance have been studied. The responses in experimental situations have corroborated clinical observations.

VASOMOTOR DISTURBANCE AND EDEMA ASSOCIATED WITH CEREBRAL HEMIPLEGIA

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It has long been recognized that partial or complete hemiplegia occurring as the result of a cerebrovascular accident is often accompanied by vasomotor disturbances and edema over the paralyzed extremities. Many clinical observations have been made and much experimental work has been performed on animals in order to determine the nature and mechanism of these disturbances since Chevallier [1] published his thesis on this subject in 1867. In recent communications Brickner,[2] Olsen [3] and Bucy [4] have thoroughly discussed the literature on the subject. Summarizing the available evidence, one reaches the following conclusions regarding the observations concerning peripheral vascular and vasomotor changes in human beings:

1. As a rule the blood pressure in the paralyzed arm is not significantly or constantly altered in comparison with that on the normal side. Both higher and lower readings have been recorded, and some observers have contended that the blood pressure is lower during the initial, flaccid, stage of the paralysis and higher in the late, spastic, stage.

2. Measurements of the temperature of the skin likewise have shown discrepancies between the two sides, both high and low readings having been obtained, the former frequently in the early stage and the latter in the late, spastic, stage.

3. Physical examination has revealed in most cases relaxed, dilated peripheral arteries on the affected side, although there are a few reports

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1. Chevallier, P. E.: De la paralysie des nerfs vaso-moteurs dans l'hémiplégie, Thèse de Paris, no. 175, 1867.

2. Brickner, R. M.: Certain Characteristics of the Cortical Influence over the Sympathetic Nervous System in Man, J. Nerv. & Ment. Dis. **71**:689, 1930.

3. Olsen, A.: Hemiplegi og hudtemperatur, Hospitalstid. **76**:1097, 1933; quoted by Kennard.[9]

4. Bucy, P. C.: Vasomotor Changes Associated with Paralysis of Cerebral Origin, Arch. Neurol. & Psychiat. **33**:30 (Jan.) 1935.

of constriction of vessels, even to the extent that the pulse was imperceptible and the digits cold and cyanotic.

4. Edema has occasionally been observed over the paralyzed extremities. Although its relationship to vasomotor disturbance has been recognized, it has not been conclusively shown whether it is due to arteriolar dilatation resulting from paresis of the sympathetic nerve supply or to arteriolar constriction with resulting stasis, as a result of stimulation of the sympathetic nervous system.

The discrepancies in the observations may be explained in part by errors inherent in the instrumental methods of examination or by differences which normally may occur between the two sides of the body. It is probable, however, that under certain circumstances either stimulation or inhibition of the sympathetic nervous system may occur in patients with hemiplegia of cerebral origin.

An extensive amount of experimental investigation in animals has contributed much knowledge toward an understanding of the influence of the cerebrum over the autonomic nervous system. In addition to the probable existence of vasomotor centers in the region of the fourth ventricle,[5] it has been shown definitely that stimulation of the hypothalamus produces the sympathetic effects [6] of an increase in the blood pressure and in the respiratory rate, dilatation of the pupil, emptying of the bladder and a decrease of intestinal peristalsis.

Evidence has been obtained that the cortex exerts a control over the vasomotor mechanism which may be concerned both with vasoconstriction and with vasodilatation. Eulenburg and Landois [7] demonstrated in 1876 that stimulation of the cortex of dogs in the region of the cruciate sulcus caused a decrease in temperature of the contralateral feet and that ablation of this region produced a rise. Pinkston, Bard

5. Ranson, S. W., and Billingsley, P. R.: Vasomotor Reactions from Stimulation of the Floor of the Fourth Ventricle, Am. J. Physiol. **41**:85, 1916.

6. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: II. Ein Sympathicuszentrum im Zwischenhirn, Arch. f. d. ges. Physiol. **135**:401, 1910; Gehirn und Sympathicus: IV., ibid. **171**:192, 1918; VII. Ueber Beziehungen der Hypothalamuszentren zu Blutdruck und innerer Sekretion, ibid. **215**:667, 1927. Ranson, S. W.; Kabat, H., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of Hypothalamus, Preoptic Region and Septum, Arch. Neurol. & Psychiat. **33**:467 (March) 1935. Beattie, J.; Brow, G. R., and Long, C. N. H.: Physiological and Anatomical Evidence for the Existence of Nerve Tracts Connecting the Hypothalamus with Spinal Sympathetic Centres, Proc. Roy. Soc., London, s.B **106**:253, 1930.

7. Eulenburg, A., and Landois, L.: Ueber die thermischen Wirkungen experimenteller Eingriffe am Nervensystem und ihre Beziehung zu den Gefässnerven, Virchows Arch. f. path. Anat. **68**:245, 1876.

and Rioch [8] reported that in both dogs and cats removal of the motor-sensory area of the cortex produced contralateral vasodilatation. On the other hand, it has recently been shown by Kennard [9] that extirpation of a certain portion of the premotor cortex in monkeys resulted in a condition in the contralateral extremities wherein there was a lag in reflex vasodilatation but that reflex vasoconstriction promptly took place. In addition, the other manifestations occurred which are typical of a lesion of the premotor area.[10] Complete removal of the remainder of the cortex in these animals resulted in no increase in the sympathetic manifestations. The blood pressures on the two sides were unchanged. Two possible hypotheses present themselves to explain the discrepancies in the reported results: Either in varying species of animals the relative dominance of the vasoconstrictor and vasodilator mechanism differs, or the completeness of the cortical lesion or its duration affects the type of response obtained.

In man the evidence is in favor of a belief that stimulation of the proper cortical regions results in contralateral vasoconstriction and that destruction produces vasodilatation. Thus, Danielopolu, Radovici and Aslan [11] found that electrical stimulation in the region of the rolandic fissure in man produced contralateral vasoconstriction. Kennard, Viets and Fulton [12] reported the case of a patient with the "premotor syndrome" due to a tumor who showed vasodilatation on the contralateral side both before and after removal of the tumor.

The present study was undertaken to gain further information regarding the nature and extent of changes in the vascular state and in the blood flow in the affected extremities of patients suffering from hemiplegia of cerebral origin and to determine the nature of the edema

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8. Pinkston, J. O.; Bard, P., and Rioch, D. McK.: The Responses to Changes in Environmental Temperature After Removal of Portions of the Forebrain, Am. J. Physiol. **109**:515, 1934.

9. Kennard, M. A.: Vasomotor Disturbances Resulting from Cortical Lesions, Arch. Neurol. & Psychiat. **33**:537 (March) 1935.

10. Richter, C. P., and Hines, M.: The Production of the "Grasp Reflex" in Adult Macaques by Experimental Frontal Lobe Lesions, A. Research Nerv. & Ment. Dis., Proc. **13**:211, 1932. Fulton, J. F.; Jacobsen, C. F., and Kennard, M. A.: A Note Concerning the Relation of the Frontal Lobes to Posture and Forced Grasping in Monkeys, Brain **55**:524, 1932. Kennard, M. A., and Fulton, J. F.: The Localizing Significance of Spasticity, Reflex Grasping, and the Signs of Babinski and Rossolimo, ibid. **56**:213, 1933.

11. Danielopolu, D.; Radovici, A., and Aslan, A.: Einfluss der Hirnrinde auf die Vasomotoren, Ztschr. f. d. ges. Neurol. u. Psychiat. **132**:671, 1931.

12. Kennard, M. A.; Viets, H. R., and Fulton, J. F.: The Syndrome of the Premotor Cortex in Man: Impairment of Skilled Movements, Forced Grasping, Spasticity and Vasomotor Disturbance, Brain **57**:69, 1934.

which is frequently observed. In part, the results of this study have previously been reported in abstract.[13]

MATERIAL

Thirty-five patients, ranging in age from 35 to 72 years, were studied. Twenty-five were males and ten females; twenty-one suffered from arterial hypertension, and fourteen had a normal blood pressure. In four cases the studies were carried out on two or more occasions. The duration of the paralysis in these cases varied from one day to thirteen years. Seventeen patients were investigated within ten days of the onset of the paralysis; ten after from ten to thirty days, and seven, after from one to six months. The remaining patient had had hemiplegia for thirteen years.

Eighteen of the patients had complete paralysis of both the arm and the leg; in seven more the arm was completely paralyzed, and the leg was affected but to a lesser extent; in two with complete paralysis of the arm the leg was normal. Four of the subjects had marked but not absolute loss of function of both the arm and the leg, and in the remaining four the arm and the leg were only moderately involved.

Twenty of the patients showed a diminished and thirteen an increased muscle tone on the affected side; in two the tone appeared normal.

RESULTS

Blood Pressure (table 1).—The blood pressure was determined for the brachial artery of each arm by the auscultatory technic with a Riva-Rocci sphygmomanometer. There was a difference of less than 10 mm. of mercury between readings of the blood pressure in the two sides in twenty-seven cases; in two the systolic or diastolic pressure was from 10 to 20 mm. higher on the normal side, and in four it was higher on the paralyzed side. There was a difference of 25 mm. of mercury between the readings of the systolic pressure in two cases; in one it was higher and in the other it was lower in the normal arm. These variations are of no special significance, as a similar degree of variation may occur in normal subjects.[14]

Blood Flow (table 1).—An estimation of the extent of blood flow in the arms and legs was made by determining the difference in the oxygen content between arterial blood and blood drawn without stasis from both antecubital and both femoral veins. In all cases the patient had been resting in the recumbent position for at least one-half hour. It being assumed that there is no great difference in the oxygen requirements of the two sides, then a lesser arteriovenous oxygen content difference on one side represents a more rapid flow of blood.[15] In six normal persons used as controls the arteriovenous differences between the two sides in both the arm and the leg were less than 2 volumes per cent.

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13. Weiss, Soma, and Ellis, L. B.: The Circulatory Mechanism and Unilateral Edema in Cerebral Hemiplegia, J. Clin. Investigation **9**:17, 1930.

14. Korns, H. M., and Guinand, P. H.: Inequality of Blood Pressure in the Brachial Arteries, with Especial Reference to Disease of the Arch of the Aorta, J. Clin. Investigation **12**:143, 1933.

15. Weiss, Soma, and Ellis, L. B.: Oxygen Utilization and Lactic Acid Production in the Extremities During Rest and Exercise, Arch. Int. Med. **55**:665 (April) 1935.

TABLE 1.—*Arterial Blood Pressure, Arteriovenous Oxygen Difference, Basal Metabolic Rate and Extent of Edema in Thirty-Five Patients with Cerebral Hemiplegia*

Case	Age	Duration of Hemiplegia	Paralysis		Muscle Tone	Arterial Blood Pressure, Mm. of Mercury		Arteriovenous Oxygen Difference, Vols. %				Basal Metabolic Rate, %	Edema	
								Arm		Leg				
			Arm	Leg		Normal Side	Paralyzed Side	Normal Side	Paralyzed Side	Normal Side	Paralyzed Side		Arm	Leg
1	72	6 weeks	++++	0	— —	.....	.....	5.5	4.0	....	....	....	+++	0
2	60	7 days	++++	++++	— —	170/122	170/120	4.6	3.0	6.1	5.3	....	++	+
		41 days	++++	++++	+ +	170/120	.....	11.1	8.5	....	....	−15		
		43 days	++++	++++	— —	145/100	160/105	....	....	....	....	−16		
3	58	3 weeks	++++	++++	— —	250/125	260/130	....	....	....	....	....	++	±
4	69	6 weeks	++++	++++	— —	206/104	198/100	8.4	2.1	10.2	6.3	−12	++	+
5	55	4 days	++++	++++	— —	210/120	210/120	3.4	2.9	....	....	+13	++	0
6	46	4 days	++++	++	+	210/110	210/100	4.9	3.2	7.6	6.1	....	+	0
7	71	3 days	+++	+++	— —	195/120	190/110	12.6	3.4	10.3	9.1	− 5	+	0
8	61	1 day	+++	+++	+ +	220/110	220/110	0.5	0.9	3.7	3.0	....	+	0
9	60	2 days	++++	++++	— —	190/100	190/100	....	7.4	....	....	....	+	0
10	63	4 days	++++	+++	— —	170/100	170/100	8.1	4.0	....	....	+ 5	+	0
11	49	3 weeks	++++	+++	— —	162/104	160/100	6.2	0.7	....	....	+14	+	0
12	39	5 weeks	++++	++++	— —	134/ 90	134/ 92	....	....	10.8	4.5	−18	+	0
13	70	9 days	+++	+++	+ +	155/ 80	155/ 75	7.0	3.4	7.3	6.2	....	+	0
		30 days	+	+	+	155/ 70	.....	....	....	7.0	3.2	....	0	0
14	60	3 days	++++	++++	+ +	168/112	170/115	6.4	0.2	6.3	5.3	....	0	0
15	35	5 days	++++	++++	— —	148/ 50	154/ 48	5.1	0.8	....	....	+26	0	0
16	52	1 day	++++	++++	+ +	190/115	195/117	4.7	2.1	....	....	....	..	..
17	46	3 days	++++	++++	— —	140/100	138/100	14.6	0.0	13.9	8.1	....	..	..
		17 days	++++	++++	— —	.....	.....	12.2	5.0	8.0	3.3			
18	48	3 days	++++	++++	— —	100/ 75	105/ 75	6.1	2.1	5.5	8.2	....	..	..
19	70	4 days	++++	++++	— —	180/ 80	190/ 95	8.1	2.4	4.8	3.7	....	..	..
20	58	5 days	++++	+	+ +	128/ 90	122/ 90	13.3	4.1	10.7	11.2	+ 2	..	..
21	65	1 week	++++	0	— —	185/120	174/120	5.8	2.7	8.9	6.8	+ 2	..	..
22	50	10 days	++++	++++	— —	125/ 90	128/ 90	8.4	5.4	10.1	13.1	....	..	..
23	55	10 days	++++	++++	— —	185/120	181/120	3.1	1.8	4.8	4.8	— 2	..	..
24	64	2 weeks	+++	++	+ +	.....	.....	10.5	8.4	9.7	....	....	..	..
25	63	3 weeks	++++	++	—	135/ 70	140/ 70	9.6	7.6	....	....	....	..	..
26	34	22 days	++++	++	Normal	92/ 65	94/ 64	5.8	3.0	7.0	4.0	....	..	..
27	60	4 weeks	++++	++++	+ +	160/105	160/105	2.3	0.7	0.6	2.9	....	..	..
28	52	1 month	++++	++++	— —	205/110	210/120	3.5	2.6	3.7	0.5	+22	..	..
29	41	1 month	++++	+	±	124/ 74	148/ 78	4.6	0.4	3.0	1.4	....	..	..
30	36	1 month	++++	++++	— —	130/ 85	.....	3.8	1.6	....	....	....	..	..
31	52	5 weeks	+++	++	+	126/ 72	.....	....	....	....	....	−18	..	..
32	55	9 weeks	+++	+	+	145/100	.....	1.9	0.2	0.0	1.2	....	..	..
33	65	4½ months	++++	++++	+ +	130/ 60	130/ 60	5.4	3.2	3.7	5.4	−17	..	..
		5½ months	++++	++++	+ +	.....	.....	10.7	4.2	3.1	2.5	+ 7		
34	43	5 months	+	+	Normal	225/140	195/135	....	....	6.4	8.7	— 5	..	..
35	50	13 years	+++	+++	+ +	110/ 72	105/ 70	7.6	3.9	5.9	4.7	....	..	..

Arm: In every case, with the possible exception to be noted, the arteriovenous difference in the normal arm was greater than that in the paralyzed arm; i. e., the blood flow over the paralyzed side was more rapid. The exception was in the case of a moribund patient (case 8) in a comatose state, in whom the arteriovenous difference in the normal arm was 0.5 volumes per cent and in the paralyzed arm 0.9 volumes per cent. It is obvious that there must have been a widespread and bilateral lowering of the peripheral resistance in the arms with a rapid blood flow, since the venous blood on each side contained nearly as much oxygen as did the arterial blood.

No correlation was found between the degree of difference in the blood flow on the two sides and the extent of paralysis, its duration, the blood pressure, the amount of peripheral arteriosclerosis or the muscular tone. In the patients in whom the determinations were repeated at a later date the difference in blood flow still existed, even though the muscle tone may have changed from flaccid to spastic and the muscular paralysis had partially cleared; hence the tonus of the musculature cannot be held responsible for the changes observed.

Leg: Although a decreased arteriovenous difference on the paralyzed side was found with much less regularity in the leg than in the arm, nevertheless it occurred in eighteen of the twenty-seven patients studied.

TABLE 2.—*Oxygen Differences Between Arterial Blood and Blood from the Internal Jugular Vein in Six Patients with Cerebral Hemiplegia*

Case	Arteriovenous Oxygen Difference	
	Normal Side, Vols. %	Paralyzed Side, Vols. %
1	2.2	3.2
2	5.8	5.6
9	7.8	8.5
10	8.6	7.1
11	5.2	5.8
14	9.8	9.5

Head (table 2): In six cases blood was obtained from the internal jugular vein on each side. In none of these cases was there any significant discrepancy between the arteriovenous differences of the two sides.

Arterial Tone.—It was observed in many of the patients that the radial artery of the paralyzed arm appeared more relaxed and dilated by palpation than the artery of the normal arm.

Basal Metabolic Rate.—Considerable individual variation existed in the basal metabolic rate, but nearly all the rates fell within the limits of normal, and the average was precisely normal. No relationship was detected between the presence of increased or decreased muscle tonus and the basal metabolic rate. It is probable, therefore, that hemiplegia is not accompanied by an appreciable degree of alteration of the basal metabolic rate, regardless of whether it is associated with an increased or decreased muscle tonus of the affected side.

Venous Pressure (table 3).—In four instances the venous pressure was determined in both arms by the method of Moritz and Tabora.[16] One of the

16. Moritz, F., and von Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsches Arch. f. klin. Med. **98**:475, 1910.

patients was suffering also from cardiac failure, and in him the venous pressure was elevated. No marked or constant difference was found between the venous pressures of the two sides. In two cases the pressure was slightly higher in the normal arm, and in one case it was slightly lower on this side; in the fourth patient the pressures were essentially equal. Villaret and Jonesco [17] found the venous pressure unchanged in patients with spastic hemiplegia but elevated in the paralyzed arm in patients with flaccid paralysis.

Cardiac Output (table 4).—Determinations of the cardiac output under basal conditions were made in two cases by the acetylene method of Grollman.[18] These were found to be normal.

Skin Temperature.—Comparative measurements of the temperature of the skin over the two sides were made for seven patients with a thermocouple. In five the temperature was definitely higher over the affected arm, and in two of the

TABLE 3.—*Venous Pressures in the Normal and Paralyzed Arms of Four Patients with Hemiplegia*

Case	Venous Pressure	
	Normal Side, Cm. of Water	Paralyzed Side, Cm. of Water
1*	20.0	17.0
2	1.0	0.5
3	5.5	4.0
4	4.0	6.5

* Decompensated.

TABLE 4.—*Cardiac Output of Two Patients with Hemiplegia*

Case	Duration of Hemiplegia	Heart Rate, per Minute	Arteriovenous Oxygen Difference, Cc. per Liter	Cardiac Output, Acetylene Method, Liters per Minute
2	41 days	76	39.0	4.9
2	43 days	74	50.5	3.7
34	5 months	73	63.7	3.2

five it was higher also over the paralyzed leg. In the remaining two cases the temperatures on the two sides were essentially alike. In five cases, including the two in which there was no difference in temperature in either the arm or the leg, measurements of the arteriovenous oxygen differences also were made and gave evidence of an increased blood flow in both the arm and the leg.

Capillary Resistance.—An estimate of the capillary resistance was obtained by applying simultaneously two suction cups over various symmetrical areas of the body for three minutes with negative pressures ranging from 80 to 200 mm. of mercury. The occurrence of petechial hemorrhages was used as a gage of the capillary breaking point. No difference in the resistance of capillaries on the two sides was noted, but it was observed that much higher pressures were necessary to produce petechiae on the legs than on the arms or the chest.

17. Villaret, M., and Jonesco, D.: Les modifications de la pression veineuse au cours des hémiplégies organiques et des séquelles des traumatismes cranio-cérébraux, Presse méd. **34**:1265, 1926.

18. Grollman, A.: The Determination of the Cardiac Output of Man by the Use of Acetylene, Am. J. Physiol. **88**:432, 1929.

Capillary Blood Flow.—The capillaries of the beds of the finger-nails on the two sides were observed in one patient, and the flow was found to be strikingly more rapid in the paralyzed hand.

Peripheral Edema.—In sixteen cases the presence or absence of edema of the hands or feet was especially looked for. Only three of the patients had no detectable edema of the paralyzed hand. In eight patients edema was definitely present, though slight in extent; four showed moderate edema of the hand and forearm, and one had extensive edema of the paralyzed arm but not of the leg. The last patient suffered also from cardiac decompensation, but he showed, nevertheless, peripheral edema only of the paralyzed arm. Edema of the paralyzed leg and foot was much less frequent: in only three of the sixteen patients was any present, and in these it was slight in extent.

COMMENT

The decreased arteriovenous oxygen difference which was found in the paralyzed arms of all our patients, and with less regularity in the legs, was almost certainly due to the increased flow of blood in these areas, for these changes occurred whether the extremities were flaccid or spastic, and there was no evidence that the metabolism of the affected side was markedly diminished. This increased blood flow occurs in all probability at the time of the cerebrovascular accident and persists for many months, if not permanently. An insufficient number of observations were made to permit the drawing of conclusions in regard to involvement of long standing, but in one patient, whose hemiplegia was of thirteen years' duration, the blood flow was still increased. It is of special interest that the increase in the blood flow is independent of the condition of the muscular tonus, occurs irrespective of the existence of arterial hypertension or peripheral arteriosclerosis and persists even when the patient has largely regained voluntary muscular power.

The increase in blood flow in the paralyzed extremities may be at the expense of the blood flow elsewhere in the body, for measurements of the total blood flow (cardiac output) failed to reveal any increase. This localized increase in blood flow appears to be due to a decreased peripheral resistance produced by arteriolar dilatation. Our observation of an elevation of the temperature of the skin over the affected area in several of the cases supports this contention. The arteries of the affected side also are involved in the vasodilatation, as evidenced by the observation of relaxed, dilated radial arteries in the paralyzed arm. It is of interest that in spite of this lowered peripheral resistance and arteriolar dilatation there is no essential difference in the arterial and venous pressures on the two sides. The lack of any significant decrease in the diastolic pressure indicates either that the peripheral resistance has not been lowered to a sufficient degree to be evident by this measure or, what is more likely, that the diastolic blood pressure is an index chiefly of the *total* peripheral resistance throughout the body, just as

the systolic pressure reflects the cardiac output exerted on this peripheral resistance. The venous pressure also is an index of the ability of the right side of the heart to take care of blood coming to it, rather than an indication of the condition of the vascular system distal to it.

That the disturbance observed in the resistance of the peripheral blood vessels in the paralyzed extremities is due to centrally acting factors is obvious because of the known nature of the cerebrovascular accident. The observation that the blood vessels of the lower extremity are less affected than those of the upper extremity is in accord with the fact, evidenced by the effects of vasomotor stimulation as well as by pharmacologic effects, that the blood vessels of the upper part of the body are much more sensitive than the vessels of the lower extremities.[19] This is seen in the flushing produced by emotional reactions, as well as by chemical agents, such as histamine, acetylcholine and epinephrine. That the difference in the sensitivity of response of the vessels of the arm is not localized only in the skin but involves also the minute vessels of the muscle is indicated by the recent study of Prinzmetal and Wilson.[20]

It is of interest that there did not appear to be any disparity in blood flow through the cerebral vessels on the two sides in the patients observed by us, although it is known that the cerebral blood vessels are sensitive to vasomotor influences.[21] Possibly a unilateral central lesion of the vasomotor center cannot produce unilateral effects in the cerebral vessels as it does in the extremities, but results either in a generalized cerebrovascular response or in none at all. It is also conceivable that the changes in blood flow resulting directly from the vascular lesion that caused the hemiplegia might be of a degree approximately equal to the reflex vasodilatation occurring on the opposite side.

As has been previously discussed, the evidence points to the fact that in human beings the cortical control of the vasomotor mechanism is dominantly vasoconstrictor; i. e., destruction of this control results in contralateral vasodilatation. In accord with this is the fact that in

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19. Weiss, Soma; Robb, G. P., and Ellis, L. B.: The Systemic Effects of Histamine in Man, with Special Reference to the Responses of the Cardiovascular System, Arch. Int. Med. **49**:360 (March) 1932. Ellis, L. B., and Weiss, Soma: A Study of the Cardiovascular Responses in Man to the Intravenous and Intra-Arterial Injection of Acetylcholine, J. Pharmacol. & Exper. Therap. **44**:235, 1932.

20. Prinzmetal, M., and Wilson, C.: The Nature of the Peripheral Resistance in Arterial Hypertension with Special Reference to the Vasomotor System, J. Clin. Investigation **15**:63 (Jan.) 1936.

21. Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: III. The Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928.

the majority of cases of hemiplegia, including not only ours but many reported in the literature, a contralateral vasodilatation is found. This is probably due to the fact that the vascular lesion which destroys the motor function also destroys the sympathetic control, either the cells in the cortex itself or the tracts in the internal capsule. It seems unnecessary to assume that a lesion of the hypothalamus or brain stem is regularly present, although injury to this area frequently is noted in the classic cases of hemiplegia. Of the patients studied by us, three subsequently came to autopsy, and all three showed lesions of the cortex or internal capsule but no evidence of involvement of the hypothalamic region or brain stem. The clinical cases of cerebrovascular accidents with evidence of marked vasoconstriction over the hemiplegic side, almost always transitory in nature, may be examples of irritation of the sympathetic pathways in the same regions which are ordinarily destroyed by the vascular lesion.

Tests of capillary resistance revealed that there is no increase in the capillary fragility in the paralyzed extremities. It is of interest, however, that on both sides of the body the capillary resistance increases progressively from the upper to the lower part of the body, requiring on the average about 80 mm. of mercury of negative pressure over the shoulders and 200 mm. over the lower part of the leg to produce capillary breakage. This is undoubtedly due to an adaptive mechanism in man, acquired by virtue of his upright posture, so that the minute blood vessels of the lower part of the body are better able to withstand the higher pressures to which they are constantly subjected.

Edema was noted to be present with great frequency over the areas where the greatest and most regular change in the resistance of the peripheral blood vessels also occurred. The most rational explanation for this edema is that it is due to an increase in hydrostatic pressure in the capillaries, caused by a widening of the arterioles and the transmission of a higher blood pressure through them, which results in an abnormally great diffusion of fluid out of the capillaries. Whether additional factors, not studied, also take part in the formation of the edema cannot be stated. This edema, therefore, is of a different nature from that of cardiac failure, which indeed also is due to increased hydrostatic pressure, but is caused by venous stasis and a raised venous pressure, with a transmission backward of this pressure to the capillaries. Of course, when hemiplegia and cardiac failure coexist, as in one of our cases, the two factors leading to edema reenforce each other, and the edema may be marked.

SUMMARY AND CONCLUSIONS

A comparative study is reported of the peripheral blood flow in the normal and paralyzed extremities in thirty-five cases of hemiplegia of

cerebral origin. The arteriovenous oxygen differences have been employed as an index of the blood flow. The blood flow in the paralyzed arm was regularly found to be greater than that in the normal arm. The blood flow in the affected leg frequently was greater than that in the normal leg but not so regularly. The differences in blood flow were independent of the extent or duration of the paralysis, of the condition of the muscular tonus or of the degree of arteriosclerosis or hypertension. In the six cases studied the cerebral blood flow was the same on the two sides.

The increase in blood flow is due to a vasodilatation involving the arteries and arterioles, resulting from altered vasomotor reflexes of cerebral origin. The possible site of involvement of the sympathetic pathways is discussed.

The temperature of the skin was higher over the affected arm than over the normal arm in five of seven patients studied, and it was higher over the affected leg than over the normal leg in two.

No significant differences in the arterial or venous pressures on the two sides were observed.

The cardiac output in two patients was normal.

The basal metabolic rate showed no consistent deviation from the normal.

The capillary resistance was not changed on the affected side but was increased on both sides in the lower extremities as compared with that in the upper extremities. This is apparently an adaptive and protective mechanism acquired by man by virtue of his upright posture, with the consequent strain on the blood vessels of the lower extremities.

Edema was noted in the paralyzed hand of thirteen of the sixteen patients observed. One factor in the formation of such edema appears to be the increase in capillary pressure due to arteriolar dilatation.

A SPECIFIC EPILEPTIC SYNDROME RELIEVED BY LYSIS OF PACCHIONIAN GRANULATIONS

PRELIMINARY REPORT OF THREE CASES

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A specific epileptic syndrome has been relieved in three instances by lysis of pacchionian granulations. This syndrome is identified clinically by the following features: 1. It is congenital, the illness first manifesting itself in each patient during infancy or early childhood and slowly progressing (in these cases for eighteen, fifty and nineteen years, respectively). 2. The convulsions occurred first in one foot (or leg), and for some years they involved only that one lower extremity, although later the attacks were frequently generalized. 3. There was (in two of the three cases) a slight underdevelopment of the leg or the side of the body where the attacks first started, without, however, any limitation of motion or true paresis of these parts. Associated with this was a slight hyperreflexia.

Cerebral exploration performed on each patient failed to reveal any pathologic lesion of the exposed brain. Electrical stimulation did, however, yield physiologic reactions of peculiar interest. Mild faradic stimuli applied along the precentral gyrus produced exquisitely focal responses, until a point was reached at which the lateral surface of the hemisphere curved over to meet the medial surface. Here in each instance was encountered, attached to the motor gyrus, a pacchionian granulation. Stimulation applied to the zone immediately surrounding this granulation produced in each patient violent generalized convulsions, having patterns identical with the preoperative convulsions. The electrical stimulation was repeated several times in each patient to assure the correctness of the observation. After this the large veins passing from the cortex through the granulations to enter the superior longitudinal sinus were doubly ligated and divided, after which the pacchionian granulations were coagulated and completely divided. The result of this was that the brain was left entirely free at this point from any attachment to the dura or to the rigid part of the calvarium.

After operation there was in each instance an immediate, substantial and (up to the time of writing) enduring amelioration of symptoms.

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Case 1.—S. G. B., a woman of 28, ill for twenty-two years, had averaged, in spite of therapy with phenobarbital, from three to four major convulsive attacks in each twenty-four hour period during her two weeks of observation in the hospital prior to operation. After the operation, performed fifteen months before the time of writing, she was entirely free from any major attack whatever for over six months. For the remaining nine months prior to this time she has averaged about one mild transient attack a month, which has occurred in each instance while she was in bed at the moment of waking from sleep.

Case 2.—M. S., a woman aged 56, had suffered from convulsions for over fifty years. At the time of her admission to the hospital, in spite of therapy with phenobarbital, she was averaging one major attack daily. These attacks were often of extremely violent nature, frequently accompanied by biting of the tongue, incontinence of the sphincters, falling and occasional serious injuries. She was operated on five months before the time of writing. Since then, although she has experienced eight or ten transient attacks of petit mal, characterized chiefly by momentary confusion, she has not had a single major epileptic attack accompanied by loss of consciousness or convulsions.

Case 3.—C. G. was a youth of 19, who had suffered from convulsions since the first year of life and had averaged during the month preceding his operation from five to ten major attacks daily in spite of large amounts of phenobarbital. Since the operation, two and one-half months before the time of writing, he has not had a single convulsive phenomenon of even the slightest nature.

Explanation of the clinical and pathologic observations made in these cases and of the rationale of the operative procedures carried out is suggested. I believe that the pacchionian granulations have two exceedingly important functions which are entirely mechanical, apart from any rôle which they may (or may not) play in the absorption of cerebrospinal fluid. In the first place, they serve as "suspensory ligaments to the brain," with a function analogous to that of the dentate ligaments of the spinal cord, "suspending" the brain from the dome of the calvarium. In the second place, they afford a necessary protection to the large veins which pass from the surface of the cerebral cortex to the superior longitudinal sinus. These veins have a large caliber and very thin walls, and unless they are "conveyed" across the subdural space by a plexus of strong nonelastic bands of tissue, any violent movement of the head may easily cause them to be torn.

The constant tugging of these firm fibrous bands comprising the pacchionian granulations on certain parts of the cortex may well be irritating to the brain; and in brains having abnormally low thresholds for stimuli they may reasonably set up zones of pathologic irritability, "trigger zones," from which epileptogenous impulses (either primary or relayed) are released. If, in addition, through some developmental anomaly, a pacchionian granulation should have its attachment to the cortex directly on a motor gyrus (as seemed to be true in the three cases reported), a mechanism would be set up peculiarly adapted for the generation of convulsive impulses.

Lysis of pacchionian granulations, as carried out in these cases, would appear to be a rational therapy for epilepsy of this type.

CONSTANCY OF THE CEREBRAL BLOOD FLOW

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Two important matters which concern the physiology of the brain are not disputed. The gray matter of the brain, in comparison to muscle, has a high rate of oxygen consumption, and a continuous supply of blood to the brain is essential. Interruption of the cerebral circulation produces loss of consciousness in six or eight seconds and permanent injury to the nerves in as many minutes. A priori, it would seem probable that the brain should be abundantly supplied with capillaries (the number of capillaries per unit of tissue is usually a gage of the metabolic activity of that tissue) and that blood leaving the brain should remain rich in the amount of oxygen which it carries.

It is, therefore, something of a surprise to learn that the number of capillaries in the gray matter of the brain is meager as compared

Average Gaseous Composition of Blood Leaving the Face, Brain, Arm and Leg of Man

Vein	Number of Samples	Oxygen Content, Percentage by Volume	Oxygen Capacity, Percentage by Volume	Oxygen Saturation, Percentage	Carbon Dioxide Content, per Cent Volumes
Internal jugular	167	12.0	19.4	61.5	54.7
Antecubital	118	13.0	20.3	64.2	52.8
Femoral	64	13.3	19.2	69.2	52.6
External jugular	40	17.8	20.5	87.0	51.2

with that of muscle [1] and that blood leaving the brain carries far less oxygen than blood leaving the face and somewhat less than blood from the extremities.[2] I now have measurements of the oxygen and carbon dioxide content of the blood from various veins of a considerable number of subjects. Values for the blood gases were determined for 167 specimens of blood from the internal jugular vein, 118 specimens of blood from a vein in the arm and 64 specimens of blood from the femoral vein. The average measurements for four regions are shown in the table. The oxygen saturation of blood leaving the tissues is least

From the Neurological Unit, Boston City Hospital, and the Department of Neurology, Harvard University Medical School. This paper is no. XLII in a series entitled "The Cerebral Circulation." The investigation was aided by a grant from the Harvard Epilepsy Commission.

1. Cobb, S., and Talbott, J. H.: Studies in Cerebral Circulation: II. A Quantitative Study of Cerebral Capillaries, Tr. A. Am. Physicians **42**:255, 1927.

2. Lennox, W. G., and Leonhardt, E.: The Oxygen and Carbon Dioxide Content of Blood from the Internal Jugular and Other Veins, Arch. Int. Med. **46**:630 (Oct.) 1930.

for the brain, most for the face and intermediate for the arm and the leg. These observations were made on patients with neurologic disorders, the majority of whom were subject to seizures. From the measurements of those who were essentially normal and from data in the literature, I believe that if the subjects were all normal the oxygen saturation of the blood in the internal jugular vein would be approximately the same as that given in the table, but the saturation of blood from the arm would be higher by approximately 8 per cent. The samples of blood from various veins were taken from the same patients but not necessarily at the same sitting. Comparison is, therefore, statistical and depends for its reliability on the number of measurements.

METHODS

Samples of blood were taken with the subjects in a lying position after a rest of fifteen minutes or longer. Puncture of the internal jugular vein was made by the method described by Myerson, Halloran and Hirsch,[3] except that care was taken to avoid stasis. Blood from a large vein at the bend of the elbow was taken without use of a tourniquet; the femoral vein was entered in the groin below Poupart's ligament. Blood was drawn under oil and chilled at once, and the blood gases were measured in the apparatus and by the method of Van Slyke.[4] The majority of the determinations were made by Mrs. Erna Leonhardt Gibbs.

DISTRIBUTION OF MEASUREMENTS

Accepting the fact that in man the average value for the oxygen saturation of blood leaving the brain is less than the average value for blood leaving the extremities, I next compared the individual measurements in order to determine their relative distribution. Data concerning the relative distribution of the oxygen saturation in blood from the brain, arm and leg are shown in the accompanying chart.

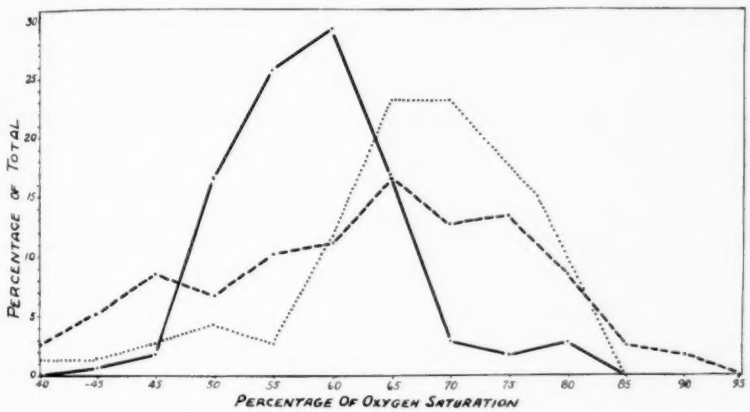
Inspection of the chart reveals that the curve representing the oxygen saturation of blood from the internal jugular vein is higher and more pointed than the curve for the oxygen saturation of blood from the vein in the arm and that for the oxygen saturation of blood from the femoral vein, indicating less scattering of the values for blood from the internal jugular vein. The contrast is greatest between this curve and that representing the oxygen saturation of venous blood from the arm. Of the specimens of blood from the internal jugular vein, 90 per cent had an oxygen saturation of between 50 and 70 per cent. Of the specimens of blood from the arm, only 54 per cent had an oxygen saturation of between 60 and 80 per cent. The curve rep-

3. Myerson, A.; Halloran, R. D., and Hirsch, H. L.: Technic for Obtaining Blood from the Internal Jugular Vein and Internal Carotid Artery, Arch. Neurol. & Psychiat. **17**:807 (June) 1927.

4. Van Slyke, D. D.: Portable Form of the Manometric Gas Apparatus and Certain Points in the Technique of Its Use, J. Biol. Chem. **73**:121 (May) 1927.

resenting the oxygen saturation of blood from the femoral vein occupies an intermediate position. I found that this relatively narrow zone of values for the oxygen saturation of blood from the internal jugular vein held good also in a smaller group of patients, from whom samples of blood from the internal jugular and basilic veins were drawn simultaneously.

Another means of judging the stability of blood flow is to take successive samples of blood from the same vein. By placing a stilet in the lumen of the needle it was found feasible to leave the needle in the vein and to draw samples of blood at intervals, thereby relieving the patient of the discomfort of repeated punctures. In four patients two samples of blood taken from the internal jugular vein at an interval of fifteen or twenty minutes yielded values for the oxygen saturation



Percentage distribution of measurements of the oxygen saturation of blood from various veins. The measurements for blood from the internal jugular vein is indicated by the solid line; those for blood from the basilic vein, by the broken line, and those for blood from the femoral vein, by the dotted line.

as follows: 63 and 63 per cent, 63 and 64 per cent, 41 and 42 per cent and 55 and 54 per cent, respectively. Successive samples taken at somewhat longer intervals from a vein in the arm of one subject yielded the following values: 65, 43, 64, 58, 59 and 52 per cent. In another subject values for successive samples were as follows: 90, 55, 69, 65 and 73 per cent. The method of successive measurements also demonstrates that blood flow is much more stable through the brain than through the arm.

COMMENT

The observed low oxygen saturation of blood leaving the brain might be ascribed to a relatively high oxygen consumption on the part of the tissues of the brain or to a relatively meager flow of blood

through the brain (due to a small vascular bed or to a slow blood flow). Data for evaluating the relative importance of these items are lacking. The observed constancy of the oxygen saturation could be due to a constancy of nerve metabolism or to a steady cerebral circulation. Here, again, there is no direct and decisive evidence. One may, however, attempt further analysis by asking two questions: First, what is the physiologic mechanism responsible for the steady state of the cerebral circulation and, second, is such a state important for the proper functioning of the brain?

Conditions which would make for a constant intracranial blood flow are: the constant temperature of the brain; the obstacle to changes of the vascular bed, consisting in the limited elasticity of the surrounding tissues; the regulation of the circulation by a special governor resident in the carotid sinus and by other nerves, and the mixture of blood effected by the circle of Willis. Against these stabilizing influences is the fact that the intracranial veins are subjected to extreme changes in pressure, for changes of posture and of intrathoracic pressure are faithfully mirrored in alterations of venous, and hence of intracranial, pressure. The observed constancy of blood flow is not a necessity. Cerebral blood flow is easily altered. In man the injection of histamine results in a greater increase in the flow of blood through vessels inside the skull than through those outside.[5] When a mixture of carbon dioxide or of carbon dioxide and oxygen is breathed, the alteration in blood flow (judging by the changes in the oxygen content of the venous blood) is three times as great in the brain as in the leg.[6] Furthermore, as was shown by the same experiments, under the stimulus of increased carbon dioxide in the blood the circulation through the brain greatly increases, coincidentally with a slight decrease or increase in the blood flow through the leg. In other words, the brain may receive a differential supply of blood, presumably favorable to its proper functioning. Because the blood flow through the brain can be made to fluctuate greatly, the fact that, with the body at rest, it does not fluctuate requires some explanation.

One possible explanation is the following: Delicate nerve tissues require not so much a high oxygen tension as a steady one, and the supply is stabilized on a lower level than that required for muscle and skin. There is evidence that the symptoms of hypoglycemia are related not so closely to the actual blood sugar level as to the rapidity of its

5. Weiss, S., and Lennox, W. G.: The Cerebral Circulation: XVII. Cerebral Blood Flow and the Vasomotor Response of the Minute Vessels of the Human Brain to Histamine, Arch. Neurol. & Psychiat. **26**:737 (Oct.) 1931.

6. Lennox, W. G., and Gibbs, E. L.: The Blood Flow in the Brain and the Leg of Man, and the Changes Induced by Alteration of Blood Gases, J. Clin. Investigation **11**:1155 (Nov.) 1932.

fall. The act of shivering is related to a fall in body temperature rather than to the degree of temperature.[7] Similarly, acute anoxemia may produce nervous symptoms not observed in states of chronic oxygen lack. In experiments on the breathing of nitrogen three subjects who had been rendered unconscious had an average oxygen saturation of 53 per cent in the arterial blood.[8] Yet the child with a congenital cardiac lesion, whose case was reported by Goldschmidt and Light,[9] had an oxygen saturation of only 45 per cent in the arterial blood and yet had no serious nervous symptoms. The unconscious subjects of the experiments on the breathing of nitrogen had a degree of anoxemia to be expected in persons instantly transported to an elevation of 16,000 feet (4,876 meters). In a balloon ascent to 29,000 feet (8,839 meters) in 1862, the two occupants, Glaisher and Coxwell, were reported to have had an ascending paralysis but to have retained consciousness. Schneider[10] found that subjects who lost consciousness quickly (from breathing nitrogen) did so without showing a preliminary fall in the blood pressure or signs of approaching collapse, whereas when anoxia was induced slowly during a half hour period about half the subjects exhibited signs indicating impending circulatory failure.

In resting muscle tissue only a small proportion of capillaries are open. Presumably, much of the fluctuation in blood flow through the uncovered arm is due to changes in the capillary bed. In the present study it was found that the circulation in the leg did not have such great fluctuations in flow, presumably because the leg, being covered and having a greater bulk of muscle, showed less variation in temperature than did the arm. This difference is shown in the chart. The vasomotor control is much weaker in the brain than elsewhere.[11] There is the further possibility that the capillary bed of the brain is always

7. Uprus, V.; Gaylor, G. B., and Carmichael, E. A.: Shivering: A Clinical Study with Especial References to the Afferent and Efferent Pathways, Brain **58**:220, 1935.

8. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: Relationship of Unconsciousness to Cerebral Blood Flow and to Anoxemia, Arch. Neurol. & Psychiat. **34**:1001 (Nov.) 1935.

9. Goldschmidt, S., and Light, A. B.: A Comparison of the Gaseous Content of Blood from Veins of the Forearm and the Dorsal Surface of the Hand as Indicative of Blood Flow and Metabolic Differences in These Parts, Am. J. Physiol. **73**:127, 1925.

10. Schneider, E. C.: A Comparison of Three Types of Anoxemia, Mil. Surgeon **54**:328, 1924.

11. Pool, J. L.; Nason, G. I., and Forbes, H. S.: Cerebral Circulation: XXXIII. The Effect of Nerve Stimulation and Various Drugs on the Vessels of the Dura Mater, Arch. Neurol. & Psychiat. **32**:1202 (Dec.) 1934.

open. Forbes[12] has not observed the opening of closed capillaries in the pia. Although there is an increase of the electrical activity of the brain before a grand mal seizure,[13] the cerebral blood flow does not change.[14] Neither are there significant differences in the blood flow through the human brain in the waking and in the sleeping state.[15] Again, the master tissue of the body can never sleep; for whether the person is sleeping or waking, resting or working, vital functions must be maintained; therefore, fluctuations in the oxygen consumption may be less for the brain than for other tissues. One might account for the low number of capillaries in the brain and for the low oxygen saturation of the blood leaving the brain by assuming that the blood has traveled slowly through capillaries that are always open, allowing time for the transfer of oxygen and nutritive materials between the blood and the brain. The conscious state of the person is not threatened till the oxygen saturation of blood leaving the brain has fallen to about 30 per cent.[8]

Would the brain function better if the oxygen tension of blood passing through the capillaries were increased? If a subject breathes air containing an increased concentration of carbon dioxide the cerebral blood flow is accelerated. In a group of five patients who breathed a mixture of 10 per cent carbon dioxide and 90 per cent oxygen the average oxygen saturation of the blood in the internal jugular vein increased from 60.4 to 84.8 per cent.[6] The results of observations made with a blood flow recorder were in keeping with these findings.[15] Rapid progress of blood through capillaries may, however, mean a decreased rather than an increased opportunity for the transfer of oxygen to the nerve tissues. The dramatic release of psychotic patients from stupor on breathing carbon dioxide, according to d'Elseaux and Solomon,[16] is not to be explained by the increased cerebral circulation. Under conditions in which the oxygen tension of arterial blood is increased by placing subjects in an atmosphere of pure oxygen or,

12. Forbes, H. S.: Personal communication to the author.

13. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133 (Dec.) 1935.

14. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man, Arch. Neurol. & Psychiat. **32**:257 (Aug.) 1934.

15. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: The Cerebral Blood Flow During Sleep in Man, Brain **58**:44, 1935; Changes in Human Cerebral Blood Flow Consequent on Alterations in Blood Gases, Am. J. Physiol. **111**:557 (April) 1935.

16. d'Elseaux, F. C., and Solomon, H. C.: The Use of Carbon Dioxide Mixtures in Stupors Occurring in Psychoses, Arch. Neurol. & Psychiat. **29**:213 (Feb.) 1933.

better still, in a compression chamber, there is a state of euphoria but a decreased rather than an increased ability to perform mental work.[17] Other tissues of the body do not function better under an excess of oxygen. Therefore, it seems not unreasonable to suppose that the brain can work best with a constant rather than with an unusually rich supply of oxygen.

It might be possible that a more widely diffused blood supply to the brain—more capillaries throughout the cortex—would improve mental activity. Is the number of capillaries per unit of cortical tissue greater in man than in animals or greater in the mentally gifted than in the stupid? Apparently this question has not been probed, although Hindzé,[18] in comparing the brains of mentally superior and of ordinary persons, found the pial vascular tree of the superior persons much more complex.

These observations and speculations are intended to be provocative. Obviously, the quantitative and comparative supply of blood to the human brain and its various portions is a problem crying for investigation.

SUMMARY AND CONCLUSIONS

Measurements of the blood gases have been made for 167 specimens of blood from the internal jugular vein, 118 specimens of blood from a vein in the arm and 64 specimens of blood from the femoral vein.

The percentage distribution of the values for the oxygen saturation of these samples indicates that the speed of blood flow is more constant in the brain than in the extremities.

It is suggested that, within limits, a constant supply of oxygen is more important to the brain than a rich supply, and the mechanism involved is discussed.

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18. Hindzé, B.: Le problème anthropologique des hommes d'élite, Bull. et mém. Soc. d'anthropol. de Paris **8**:15, 1927; Wie sollen wir die Hirnarterien verarbeiten? Zur Methodik der makroskopischen Erforschung der Hirnarterien, Ztschr. f. d. ges. Neurol. u. Psychiat. **132**:443, 1931.

Technical and Occasional Notes

QUININE: AN EFFECTIVE FORM OF TREATMENT FOR MYOTONIA

Preliminary Report of Four Cases

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I shall give a brief report of the effectiveness of quinine in the treatment of myotonia, a condition hitherto almost entirely uninfluenced by any mode of therapy. Thus far, four patients have been given quinine, with resultant relief from myotonic disturbances. Rarely does a remnant of myotonia appear after adequate dosage.

REPORT OF CASES

CASE 1.—J. D., an Italian aged 33, was admitted to the Bellevue Hospital on Nov. 1, 1935, complaining of "inability to get started quickly in any movement" which had been present since the age of 7 years. He described an initial weakness in any voluntary movement, accompanied by prolonged contraction and retarded relaxation, an "intention rigidity," which was aggravated by fatigue, emotion and cold and was relieved somewhat by heat or by a hot bath. The condition was worse in winter and better in summer. Occasionally he suffered from double vision.

Physical examination revealed large, overdeveloped muscles. Percussion of these produced sharp local contraction and slow relaxation, with the formation of a groove or furrow. Every striated muscle was affected in the aplasticity. A diagnosis of myotonia congenita was made.

CASE 2.—C. D., aged 35, a brother of J. D., had been similarly afflicted since the age of 6 years.

CASE 3.—J. P., aged 23, a sister of J. D., had had the same disease since childhood.

CASE 4.—H. P., a woman aged 21, exhibited slight atrophy of the sternocleidomastoid muscles and marked atrophy of the muscles of the forearm, notably of the extensor muscles of the fingers, the muscles of the thighs and the anterior tibial muscles. The tongue and hands showed a myotonic reaction. In spite of the patient's youth a diagnosis of myotonia atrophica was made.

Thomsen,[1] who first adequately described this disease, in 1876, recommended vigorous exercise. Weiss and Kennedy[2] reduced myotonic

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From the Department of Neurology, service of Dr. Foster Kennedy, Chief of Staff.

Presented at the Bellevue Hospital before the New York State Medical Society, April 30, 1936.

1. Thomsen, J.: Tonische Krämpfe in willkürlich beweglichen Muskeln infolge ererbter psychischer Disposition, Arch. f. Psychol. u. Nervenh. **6**:702, 1876.

2. Weiss, S., and Kennedy, Foster: Clinical Experiments in Myotonia Congenita (Thomsen) with Especial Reference to the Parasympathetic Nervous System, Arch. Neurol. & Psychiat. **11**:543 (May) 1924.

phenomena in one instance by administering thyroid followed by atropine. Pamboukis [3] obtained relief in some cases by the administration of posterior pituitary, calcium chloride and acetylsalicylic acid. Lindsley and Curnen [4] reported a reduction in the amount and duration of the after-contraction following the administration of calcium gluconate and calcium chloride. None of these remedies was effective in reducing the myotonia of the patients reported on here.

Various stimulants and depressants of the autonomic nervous system were tested but proved of no value. When these were exhausted, several alkaloids were evaluated. The most remarkable effect was obtained from quinine. Ten grains (0.648 Gm.) of quinine di-hydrochloride, injected intravenously, abolished every myotonic phenomenon within ten minutes, the effect lasting from fifteen to twenty hours. Quinine hydrochloride, from 5 to 10 grains (0.324 to 0.648 Gm.), given by mouth two or three times a day, proved to be an adequate maintenance dose. Just how the drug acts in this disease is not clear.

It is known that quinine produces a transient increase in the power of skeletal muscle, followed shortly by fatigue and weakness of contraction, that it produces vascular dilatation and is an antagonist to epinephrine, that it depresses the vagus terminations and that it diminishes reflex action.[5]

Recently, Lindsley and Curnen [4] presented evidence for the hypothesis that the after-contraction of myotonia is of reflex origin and is due to the persistent discharge of hyperexcitable sensory end-organs in muscle. In the light of their report it would seem that quinine is effective against myotonia through its diminution of reflex action. Further studies on the behavior of quinine are being carried out with other patients.

CONCLUSION

Quinine is a specific for myotonia.

3. Pamboukis, B.: Bemerkungen über einige myotonische Zustände, Schweiz. Arch. f. Neurol. u. Psychiat. **26**:84, 1930.

4. Lindsley, D. B., and Curnen, E. C.: An Electromyographic Study of Myotonia, Arch. Neurol. & Psychiat. **35**:253 (Feb.) 1936.

5. Potter, S. O. L.: Therapeutics, Materia Medica and Pharmacy, revised by R. J. E. Scott, ed. 15, Philadelphia, P. Blakiston's Son & Co., 1931.

Case Reports

MULTIPLE HEREDITARY HEMANGIOBLASTOMAS OF THE NERVOUS SYSTEM

PAUL M. LEVIN, M.D., BALTIMORE

Angiomatosis of the nervous system has been recognized as a peculiar type of developmental defect since the original and important contribution of Lindau.[1] He called attention to the association of Hippel's disease (angiomatosis retinae) with angiomatous tumors of the cerebellum and other parts of the central nervous system and with a variety of systemic abnormalities, particularly pancreatic and renal cysts and hypernephroid tumors of the kidney. He considered these lesions to be the result of a perverted development of the mesodermal germinal layer, beginning probably in the third month of fetal life. The clinicopathologic contribution has been amply confirmed by many observers. As further evidence of the anomalous developmental nature of Lindau's disease cases have been described in which the condition is hereditary and in which multiple hemangioblastomas have been found in the central nervous system.

The case reported here is such a one. There was a family history of probable intracranial tumor, and multiple hemangioblastomas and a cerebellar cyst were found at operation, thus verifying a preoperative diagnosis of Lindau's disease.

REPORT OF A CASE

L. S., a woman aged 19, was first treated in this hospital in 1930, when a diagnosis of acute sacro-iliac arthritis was made. Because of pains and twitchings of the left leg, a neurologic consultation was requested; it yielded entirely normal results. Application of a body cast brought about relief, and the patient remained well until toward the end of 1934.

Early in December 1934 the patient noticed beginning lassitude and general weakness; these symptoms were soon followed by marked drowsiness. She slept whenever she sat down or rested but did not sleep during meals or while she was walking. There was no cataplexy. Several weeks later she began to have sudden attacks of sharp pain in the fronto-occipital region, associated with projectile vomiting which frequently relieved the pain. There were a few attacks

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From the Division of Neurology and Neurosurgery, University of Chicago Clinics.

Read at a meeting of the Chicago Neurological Society, May 16, 1935.

1. Lindau, A.: Studien über Kleinhirncysten; Bau, Pathogenese und Beziehungen zur Angiomatosis Retinae, Acta path. et microbiol. Scandinav., supp. 1, 1926, p. 1.

of vertigo with a sense of rotation of the head. She came to the outpatient department of the clinics on Jan. 28, 1935, and was immediately admitted to the hospital.

Examination.—The patient was stuporous and somewhat undernourished. Her responses were often facetious. There was retraction of the head, with moderate stiffness of the neck and a bilateral Kernig sign. The left optic disk was choked, the elevation measuring 1 diopter; the retinal veins were dilated, and numerous striate hemorrhages were present. The right optic disk showed only a mild blurring of its nasal margin. The pupils reacted well to light; the extra-ocular movements were full, and there was no nystagmus. Hearing was normal in both ears. The tendon reflexes were brisk on the right side, and the toes on this side were weaker than those on the left. There was no Babinski sign. Sensory tests indicated an impairment of sense of position and perception of vibration in the left foot. Deep sensibility was normal in the hands. Coordination in the extremities was fairly good; the gait was unsteady and on a wide base. There were frequent extrasystoles, which electrocardiographically appeared to be of auricular origin. A mass was palpable in the region of the lower pole of the right kidney. There was mild scoliosis in the lumbar region.

The temperature was normal, as were routine blood counts and the results of urinalysis and of Wassermann and Kahn tests on the blood. Roentgenograms of the skull revealed only an anomaly of the dural sinuses, the superior longitudinal sinus deflecting to the right in its posterior fourth and communicating only with the right lateral sinus. Medial to the deflected longitudinal sinus there was an area, about 3 cm. in diameter, of unusual thinness of the occipital bone.

Because of the vague clinical picture and outspoken signs of meningeal irritation, a diffuse involvement of the meninges was suspected. Such pictures have been seen in cases of infection with Torula or sarcomatosis of the meninges. A lumbar puncture was made cautiously. The cerebrospinal fluid was slightly yellow and not turbid, and the pressure was 380 mm. of water. The Queckenstedt test indicated possibly a slight spinal subarachnoid block. There was a moderate excess of globulin, as shown by the Pandy test. The cell count was 1 lymphocyte per cubic millimeter. The Wassermann reaction of the spinal fluid was negative. Whenever a few drops of fluid escaped, the patient complained of violent suboccipital pain; therefore, only a small amount of fluid was withdrawn.

On the basis of this information the diagnosis was changed to that of intracranial tumor, probably intraventricular. The early onset of drowsiness suggested possibly a tumor of the third ventricle, and the stiffness and retraction of the neck, a localization in the fourth ventricle. In order to arrive at accurate localization, ventriculography was performed. This disclosed a dilatation of the entire ventricular system down to the middle of the fourth ventricle. The cerebral aqueduct was angulated and displaced anteriorly.

Family History.—At this time it was learned that in 1910, at the age of 24, the patient's father was taken ill with severe headaches and vomiting. At St. Luke's Hospital in March of that year Dr. Albert E. Halstead performed a subtemporal decompression which relieved these symptoms. The decompression was at times flat, and then the man felt well; when it bulged he felt "dopey" and "dizzy." The only constant symptom was an inability to feel objects with his left hand. Later there developed difficulty in walking. In 1917 he gradually failed and died. Verification of the tumor was not made. His sister had died in 1894 at the age of 16 years after an illness of two years. Her symptoms had been

failure to menstruate, severe headaches and loss of hair. No member of the family suffered from any visual defect. Another paternal aunt of the patient and her ten children were all apparently well.

Repeated careful examination of the ocular fundi revealed no evidence of angiomatosis of the retina, but in view of the family history and of the localization of the patient's tumor in the posterior fossa, a diagnosis of Lindau's disease was made.

Operation.—The diagnosis was verified at a suboccipital craniectomy performed by Dr. Paul C. Bucy on Feb. 7, 1935. The cerebellum was tense, and before the dura mater was incised widely a needle was introduced into the left hemisphere. Fortunately it encountered a large cyst containing yellow, clotting fluid. The dura mater was then opened (fig. 1). The wall of the cyst was smooth

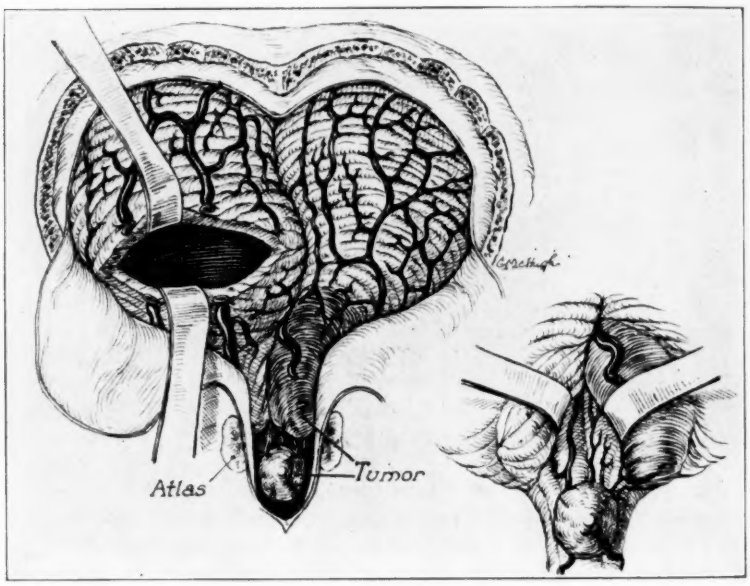

Fig. 1.—Drawing elaborated from a postoperative sketch by the operator. It shows the cyst in the left cerebellar hemisphere, the tumor of the right tonsil of the cerebellum and the tumor nodule presenting over the posterior surface of the upper cervical cord.

throughout, and no sign of a mural tumor was found. The tonsils of the cerebellum were herniated through the foramen magnum, necessitating removal of the arch of the atlas. The right tonsil was considerably enlarged and grayish red. Immense vessels entered it, carrying bright red blood. On the dorsal surface of the first cervical segment of the spinal cord lay firmly attached a highly vascular tumor nodule, about 12 mm. in diameter, which also had numerous large vascular connections. A biopsy was made of the tonsillar lesions, and the wound was closed.

Postoperative Course.—The postoperative course was satisfactory. Bilateral nerve deafness of moderate degree and palsy of the right abducens nerve, which

had appeared following ventriculography, gradually improved, and the optic disks flattened. The extrasystoles disappeared. The abdominal mass was shown by pyelography to be a normal, although displaced, kidney. The patient was discharged on March 6, 1935. A month later she returned to the clinic feeling quite well.

Microscopic Examination of the Tumor.—The tumor was a capillary hemangioblastoma (fig. 2). It was moderately cellular. The cells were usually elongated, with cell processes merging into a network of reticulin. There was an abundance of thin-walled capillary spaces the walls of which were formed by the tumor cells. Most of these capillaries were empty. There were few interstitial cells. Silver impregnations for connective tissue showed an abundant reticulum, mostly in the walls of the labyrinth of vessels. No mitoses were seen.

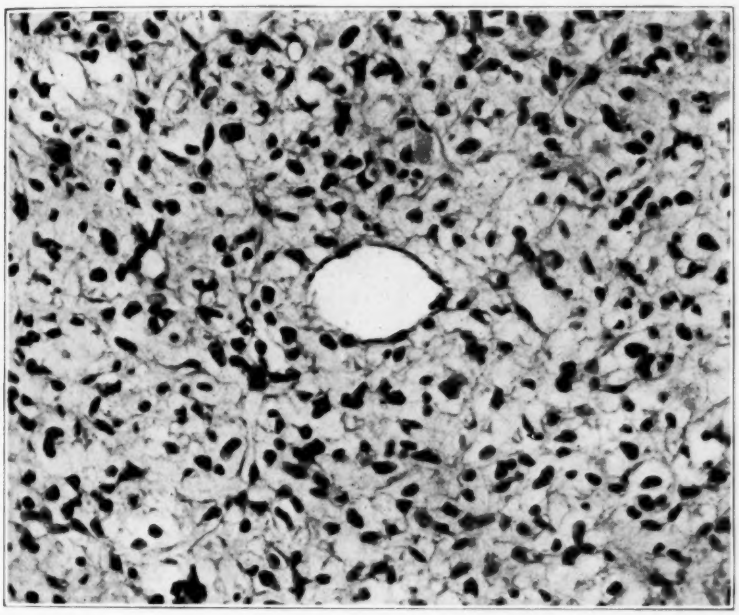

Fig. 2.—Photomicrograph of a section of the tumor, stained with hematoxylin and eosin; × 300.

COMMENT

Although it was thought that the clinical findings pointed to a tumor in the region of the fourth ventricle, ventriculography was used to establish the localization because the early history of drowsiness indicated a possibility that the lesion was situated in the third ventricle. The information concerning the illnesses of the patient's father and aunt was not obtained until after a ventriculogram had been made. Had it been available earlier, ventriculography could have been avoided. The symptoms exhibited by the patient's father were typical of cerebellar hemangioblastoma, namely, intermittent symptoms of increased intracranial pressure, paucity of signs of cerebellar involvement and

occasional ipsilateral astereognosis (Cushing and Bailey [2]). The symptoms shown by the aunt were not as definite, but nevertheless suggested more the diagnosis of intracranial tumor than that of any other disease. Although no angioma of the retina could be seen in my patient, the diagnosis of hemangioblastoma was made from the age of the patient, the location of the lesion in the posterior fossa and the family history. The suspicion that visceral anomalies were present, based on the finding of the abdominal mass, was not substantiated when pyelography demonstrated a normal kidney.

The failure to find tumor tissue on inspection of the wall of the cerebellar cyst is not a new experience. Others have had the same difficulty at operation [3] or even at autopsy,[4] although it is possible that in some of these cases microscopic examination of the entire cyst wall might have disclosed a small nest of tumor tissue. The spinal tumor at the first cervical segment was probably responsible for the partial spinal block. Another, undiscovered, spinal lesion may have been responsible for the pain in the lower part of the back and the left leg, and possibly for the scoliosis.

One may make a preoperative pathologic diagnosis of a hemangioblastoma with precision when angiomatosis retinae is present. Möller [5] and Viets [3] were able thus to predict the nature of the tumor in their cases. When a family history is all that is available, the diagnosis is not as certain. Other lesions may be hereditary. In cases of pontile telangiectasis there may be a history of tumor of the brain among the relatives, as in a case which my co-workers and I have studied, in which the anatomic findings established the diagnosis,[6] and also in the clinical case of Kufs.[7] One may also be misled by a case such as that which Lindau [1] observed (case 20) in which a cerebellar gliomatous cyst occurred in the daughter of a woman who had died of what was found at necropsy to be a chronic cerebellar abscess. However, a characteristic history, such as was given for my patient's father, justifies at least a presumptive diagnosis of the pathologic nature of the tumor.

The occurrence of this condition in different members of a family was first noted in 1893 by Collins,[8] who found angiomatosis retinae in

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2. Cushing, H., and Bailey, P.: Tumors Arising from the Blood Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas, Springfield, Ill., Charles C. Thomas, Publisher, 1928.

3. Viets, H. R.: An Additional Case of Hemangioblastoma of the Retina and Cerebellum, with a Note on Lindau's Disease, J. Nerv. & Ment. Dis. **77**:457, 1933.

4. Friedrich, H., and Stiehler, H.: Ein Hämangioendotheliom der Medulla oblongata, Deutsche Ztschr. f. Nervenh. **73**:158, 1922.

5. Möller, H. U.: Familial Angiomatosis Retinae et Cerebelli—Lindau's Disease, Acta ophth. **7**:244, 1929.

6. This and other cases of hereditary telangiectasis of the brain will be reported in a forthcoming paper by Dr. Joseph C. Michael and me.

7. Kufs, H.: Ueber heredofamiliäre Angiomatose des Gehirns und der Retina, ihre Beziehungen zueinander und zur Angiomatose der Haut, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:651, 1928.

8. Collins, E. T.: Two Cases, Brother and Sister, with Peculiar Vascular New Growth, Probably Primary, Affecting Both Eyes, Tr. Ophth. Soc. U. Kingdom **14**:141, 1894.

a brother and sister. That likewise the hemangioblastomas of the nervous system are hereditary might have been suspected from the observation made in 1872 by Hughlings Jackson [9] of a cystic yellow tumor of the cerebellum in a girl, aged 20, whose sister had died after four days of coma following a third convulsion. The dependence of the disease on genetic factors is now widely recognized. Such familial incidence occurs, according to Lindau,[10] in 20 per cent of cases. Thomsen,[11] from a study of affected families, proved that the transmission of the disease occurs by a simple dominant factor, not sex-linked.

Such hereditary influences have been reported by Seidel,[12] Tresling,[13] Brandt,[14] Rochat,[15] Möller,[5] Cushing and Bailey,[2] Collier,[16] Vincent and Rappoport,[17] Knodel,[18] Martin and van Bogaert,[19] Wolf and Wilens [20] and Panà.[21] The most extensive familial incidence is that described by Möller, in which six cases of single or combined retinal and cerebellar tumors occurred in three generations. It was in one of these cases that Möller was able for the first time to make the diagnosis of an intracranial hemangioblastoma preoperatively. Knodel's patient was the daughter of Hippel's original patient with angioma of the retina. In the daughter a retinal angioma of microscopic size was found.

Survey of the reported cases in which multiple hemangioblastomas were found in the nervous system yields some interesting information. At least sixteen such cases are reported in the literature, in all of which the multiplicity of tumors was discovered at autopsy. These

9. Jackson, Hughlings: A Series of Cases Illustrative of Cerebral Pathology: I. Cerebral Tumors, M. Times & Gaz. **2**:541 and 568, 1872.

10. Lindau, A.: Discussion on Vascular Tumors of the Brain and Spinal Cord, Proc. Roy. Soc. Med. (Sect. Neurol. & Sect. Ophth.) **24**:363, 1930.

11. Thomsen, Oluf, cited by Möller.[5]

12. Seidel, E.: Ueber ein Angiom der Netzhaut, Ber. ü. d. Versamml. d. ophth. Gesellsch. **38**:335, 1913; cited by Lindau.[1]

13. Tresling, J.: Ueber Angiomatosis Retinae, Klin. Monatsbl. f. Augenh. **64**:306, 1920.

14. Brandt, R.: Zur Frage der Angiomatosis Retinae, Arch. f. Ophth. **106**: 127, 1921.

15. Rochat, G. F.: Familiäre Angiomatosis Retinae und Kleinhirnangiom, Klin. Monatsbl. f. Augenh. **78**:601, 1927.

16. Collier, W. T.: Two Cases of Lindau's Disease, Brit. M. J. **2**:144, 1931.

17. Vincent, C., and Rappoport, F.: Deux cas d'hémangioblastome du cervelet dont l'un familial. Sur la valeur de l'attitude de la tête pour le diagnostic des tumeurs de la fosse postérieure, Rev. neurol. **1**:32, 1931.

18. Knodel, G.: Zur Kenntnis der v. Hippelschen Erkrankung (Angiomatosis Retinae), Virchows Arch. f. path. Anat. **281**:886, 1931.

19. Martin, P., and van Bogaert, L.: Deux cas d'hémangiome du cervelet chez deux soeurs, J. belge de neurol. et de psychiat. **33**:809, 1933.

20. Wolf, A., and Wilens, S. L.: Multiple Hemangioblastomas of the Spinal Cord with Syringomyelia, Am. J. Path. **10**:545, 1934.

21. Panà, C.: Su la morfologia e la istogenesi degli angioreticulomi encefalici. (Morbo di Lindau in due fratelli), Riv. di pat. nerv. **44**:1, 1934.

cases were reported by Koch,[22] Wersilow,[23] according to Lindau's[1] interpretation, Brandt,[14] Friedrich and Stiehler,[4] Tannenburg,[24] Lindau[1] (cases 12 and 28), Schuback,[25] Sladden,[26] Rochat[27] (two cases, in brothers), Kernohan, Woltman and Adson,[28] Wolf and Wilens,[29] Hughes[29] and and Panà[21] (two cases, in brothers).[30] As in some of these cases a complete autopsy was not performed, I may include my case, in which only the posterior fossa was exposed at operation. This gives a total of seventeen cases.

The rhombencephalon was examined in the seventeen cases. The cerebellum was the seat of one or more tumors in sixteen of the cases, and the medulla oblongata and pons were involved in six. In the one case in which a cerebellar tumor was not found there was a large angioma in the fourth ventricle growing from the floor. One of the cerebellar lesions was a cyst, the walls of which contained no tumor (only glia). The spinal cord was examined in ten cases; in each of these it contained one or more tumors, either within the substance of the cord or in the nerve roots. In one case[27] a large tumor was present in one cerebral hemisphere, mainly in the basal nuclei and the temporal lobe. In five cases the retinas either showed angiomas or had previously become detached. In one case[27] both eyes were removed and sectioned serially but an angioma was not found. The viscera were examined in ten cases, in all of which anomalies typical of Lindau's disease were present. In one[14] of these there were also multiple angiomas of bones (vertebrae, ribs and petrous pyramid).

Thus, in every case of multiple hemangioblastomas of the central nervous system tumors were found in the spinal cord and viscera as well as in the rhombencephalon when proper examination was made.

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22. Koch, K.: Beiträge zur Pathologie der Bauchspeicheldrüse, Virchows Arch. f. path. Anat. **214**:180, 1913.

23. Wersilow, W.: Zur Frage über die sogen. serösen Zysten des Kleinhirns, Neurol. Centralbl. **32**:350, 1913.

24. Tannenburg, J.: Ueber die Pathogenese der Syringomyelie, zugleich ein Beitrag zum Vorkommen von Capillarhämangiomen im Rückenmark, Ztschr. f. d. ges. Neurol. u. Psychiat. **92**:119, 1924.

25. Schuback, A.: Ueber die Angiomatosis des Zentralnervensystems (Lindausche Krankheit), Ztschr. f. d. ges. Neurol. u. Psychiat. **110**:359, 1927.

26. Sladden, A. F.: A Case of Lindau's Disease (Capillary Angiomatosis), Brit. J. Ophth. **14**:224, 1930.

27. Rochat, G. F.: Familiäre Angiomatosis Retinae und Kleinhirnangiom, Klin. Monatsbl. f. Augenh. **78**:601, 1927.

28. Kernohan, J. W.; Woltman, H. W., and Adson, A. W.: Intramedullary Tumors of the Spinal Cord: A Review of Fifty-One Cases, with an Attempt at Histologic Classification, Arch. Neurol. & Psychiat. **25**:679 (April) 1931.

29. Hughes, R. F.: A Case of Lindau's Disease, Canad. M. A. J. **31**:537, 1934.

30. In the review by J. G. Greenfield (The Pathological Examination of Forty Intracranial Neoplasms, Brain **42**:29, 1919) there is reported another case of multiple hemangioblastomas of the cerebellum, so diagnosed from histologic preparations by Cushing and Bailey.[2] It is noted in the clinical report of this case (case 10) that an "elder brother and younger sister died 'of the same thing.'"

The frequency with which spinal hemangioblastomas occurred in this series is unexpected in the light of previous knowledge.

The importance of the spinal lesions is not paralleled by the number of reported cases of solitary tumors in this location. The chief reason for this paucity of reports probably is the difficulty in making a pathologic diagnosis. Many of the lesions are associated with cysts of the spinal cord. These cysts are lined by glia and often contain nests of proliferating ependymal cells [28] or glia cells.[18] The lesions may then be termed merely syringomyelia or else intramedullary tumors (ependymomas or astrocytomas) with secondary cystic formations. Possibly a small number of lesions are considered as angiomatous malformations of the meninges, an underlying intramedullary hemangioblastoma being overlooked. Such a hemangioblastoma of the spinal cord with extreme varicosities of meningeal vessels was reported by Guillain, Schmite and Bertrand.[31] Furthermore, since these tumors not infrequently fail to produce symptoms, their presence may not be suspected and they may escape attention both during life and at necropsy.

SUMMARY

A case of multiple hemangioblastomas of the central nervous system is reported in which a pathologic diagnosis was made preoperatively on the basis of the family history and of the location of the tumors. A survey of reports of multiple hemangioblastomas in the nervous system reveals unexpectedly the occurrence of tumors in every spinal cord examined. This suggests that the occurrence of hemangioblastoma of the spinal cord is more frequent than has hitherto been realized.

31. Guillain, G.; Schmite, P., and Bertrand, I.: Hémangiome médullaire, Rev. neurol. **1**:420, 1932.

Obituaries

CLARENCE ANDERSON PATTEN, M.D.
1890–1936

The untimely death of Dr. Clarence A. Patten on June 2, 1936, is a distinct loss to neurology in Philadelphia, to graduate teaching in the United States and to Dr. Patten's many friends. The suddenness of his passing was a painful experience not only to his family and immediate associates but to the entire membership of the American Neurological Association, which, at the time of his death, was assembled in Atlantic City for its sixty-second annual meeting.

Dr. Patten was born in Hampden, Maine, on May 8, 1890. Like his forefathers of many generations, he was raised on a farm. He attended the public schools, the Hampden Academy and the Jefferson Medical College in Philadelphia, graduating in 1916. From the beginning of his medical career he was interested in neuropsychiatry, and immediately after graduation from medical school he served as junior assistant physician in the Pennsylvania Hospital for Mental and Nervous Diseases from June 1, 1916, to Feb. 1, 1917. On Feb. 1, 1917, he began an internship at the Jefferson Hospital in Philadelphia, but he interrupted his service on July 26, 1917, to join the army. He was discharged from the army with the rank of captain on June 28, 1919. From July 1, 1919, to Jan. 1, 1920, he was senior assistant physician at the Pennsylvania Hospital for Mental and Nervous Diseases. From Jan. 1 to June 1, 1920, he returned to the Jefferson Hospital to complete his internship.

In the succeeding years he was associated with a number of institutions, which broadened his background in neuropsychiatry. He was assistant neuropathologist in the Philadelphia General Hospital from July 1920 to November 1922. He was associated with the Graduate School of Medicine of the University of Pennsylvania and with the Philadelphia General Hospital. His growth in both institutions was steady and progressive. In the Graduate School of Medicine he was appointed instructor in neurology and neuropathology on July 1, 1923, associate in neurology on July 1, 1924, assistant professor in neurology on July 1, 1926, and associate professor in neurology on July 1, 1930. He succeeded Dr. T. H. Weisenburg as professor of neurology and vice dean in neurology and psychiatry on March 11, 1935.

His wide interests in neurology and psychiatry and associated fields are well illustrated by the numerous offices he held at various times in

his career. His publications portray his versatility and his active interest in the various problems of neuropsychiatry. Among other things, he was greatly interested in the endocrine aspects of this field and in the vegetative nervous system. He was particularly concerned with the problem of cerebral birth conditions, to which he made several contributions of great value. He maintained that Little's disease includes a heterogeneous group of disorders and did much to clarify this entire problem. His views concerning the relation of this condition in many

CLARENCE ANDERSON PATTEN, M.D.
1890–1936

cases to an intra-uterine condition were important in directing attention away from the time-hallowed concept of birth injury as the cause of so-called Little's disease and represented splendid examples of good clinical research. His investigations, however, were not entirely clinical, for early in his career he wrote several papers concerned with neuropathologic subjects, notably on the vascular diseases of the brain. He made a number of contributions on infection and intoxication in the central nervous system. He had an active interest not only in all phases

of organic neurology but in psychiatry as well. He was especially interested in mental hygiene and was untiring in the various activities for the prevention of mental and nervous diseases. He served as editor in charge of neuropsychiatry of the "Cyclopedia of Medicine" and wrote a number of the chapters himself.

The motif of Dr. Patten's life was service, and the driving force, a severe New England conscience. These factors were undoubtedly responsible for his relinquishing of an ancestral farm to become a physician. His sincerity and his devotion to his work knew no limitations and were sensed immediately by those who came in contact with him. That great teacher and surgeon J. Chalmers Da Costa recognized these traits in him even when he was an intern at the Jefferson Hospital. In the United States Army General Hospital at Plattsburg he became an important factor in the management of the war neuroses. He was transferred to United States General Hospital No. 1 in New York, where his work on injuries of peripheral nerves was recognized as most comprehensive, and his opinion concerning the advisability of operation in all cases was greatly respected. It was in Plattsburg that he first met the late Dr. T. H. Weisenburg, an event of great importance to both these men, for Dr. Patten assisted Dr. Weisenburg considerably in the development of graduate teaching in neurology in Philadelphia. Despite his many and varied activities, he never lost his capacity for attention to details in the individual case or his concern for the patient. He had a great sense of responsibility concerning the keeping and appearance of hospital records. These and many other qualities distinguished him among his colleagues.

Dr. Patten was a natural leader. This was evident during his army service and in his later life as a teacher and officer of various organizations. His leadership depended on two factors: his broad vision and his ability to attract and keep friends. One of his outstanding traits was devotion to his friends. Many of his numerous acquaintances soon became his devoted and loyal friends for whom he was ready to sacrifice time and effort, adding greatly to his responsibilities and burdens, frequently at the expense of his health. He was sensitive and temperamental, and his strong sense of justice never permitted him to overemphasize his likes or dislikes.

It was as a teacher that he displayed all his outstanding qualities: breadth of vision, capacity for detail, the unusual combination of clarity and brevity, capacity for sustained interest and enthusiasm and unlimited indefatigability. His students often expressed his abilities by stating that his profound knowledge was always well diluted with good common sense. He had a fine capacity for directing research among graduate students.

Those who knew Dr. Patten intimately were aware of the fact that his constant work and his willingness to help others were associated with considerable physical suffering and perhaps pathos. He frequently concealed it by his wholesome sense of humor and his playfulness with his family and other intimates. He allowed himself too little recreation, with the exception of his annual summer holiday to his native Maine, which has become his final resting place.

On July 21, 1920, Dr. Patten married Helen Patten, of Hampden, Maine. Though in no way related to each other, they were childhood friends, and theirs was a beautiful married life. Dr. Patten is survived by his wife, a daughter, Jeanne, and two sons, Robert and Morton.

J. C. YASKIN.

News and Comment

CHILD NEUROLOGY RESEARCH

With a grant from the Friedsam Foundation a special committee or council will be formed "to stimulate Research in Child Neurology and allied fields, so that physicians and other scientists may contribute to the thorough investigation of the many problems bearing upon the care and cure of those afflicted with any of the nervous and mental disorders from birth through adolescence." This research work is to be encouraged by stipends, scholarships and other means and is not to be limited to any special groups or institutions. It is to be nation-wide in scope. The committee is to be organized by Dr. Bernard Sachs, the director. According to present plans it will consist of two neurologists, in addition to the director, two pediatricians, one orthopedist and two laymen. The "laymen" will be needed to help decide problems of a social character. "The Trustees of the Friedsam Foundation find that Neurology and Psychiatry have important relations to the early training of children, to development of character, to general medical and home conditions and agree with Doctor Sachs that the problems of Child Health and Welfare may be properly considered to be closely allied fields for investigation."

The outline of the preliminary program is as follows:

I. *Investigation of Organic and Functional Diseases of the Nervous System.*

(*a*) Prenatal conditions and influences.

(*b*) Heredity in its relation to nervous and mental disorders of childhood (accurate studies are needed). Do the mendelian laws apply to disease in man? Heredity versus environment (studies on this subject have been begun).

(*c*) Influences operative during the intra-uterine period. Effect of disease of the mother on the child. Acute infectious diseases of the mother during pregnancy. Renal and other disorders. Neurotic condition of the mother during pregnancy. Accident to the mother during pregnancy. Syphilitic disease of either parent.

(*d*) Accidents and injuries during labor and at birth. Resulting physical and mental conditions. Treatment of palsies resulting from birth and early palsies.

(*e*) Infectious diseases of early life, especially poliomyelitis and all forms of encephalitis (studies in the early diagnosis are needed). Bacteriologic and immunologic problems. Serum treatment and vaccines.

(*f*) Careful studies of all early paralytic conditions with especial reference to therapeutic methods, physical, surgical and orthopedic. Paralytic deformities. Exact studies with the aid of the orthopedist as to the use and limitation of surgical and nonsurgical procedures. Gymnastic training. Benefits of underwater treatment. (Promising contributions on these subjects are already in preparation.)

(*g*) Early defects of speech, aphasia of all types, stammering and stuttering; proper treatment and training.

(*h*) Relation of the endocrine glands to normal development and to nervous disorders (an important series of topics).

(*i*) Studies of the lipoid metabolism and its bearing on familial and other diseases.

(*j*) Careful studies on chemistry of the brain and the bearing on conditions of the brain. Also studies on the electric action currents of the brain.

(*k*) Extensive studies (already begun) on the general subject of convulsions and epilepsy in children, carried out in association with pediatricians and neurosurgeons. Also studies on choreas of organic origin.

(*l*) All the various well known types of organic and functional diseases of the spinal cord and brain, including hereditary and degenerative diseases and the progressive muscular atrophies, dystrophies and myotonias (clinical and therapeutic studies are needed). Defects of the brain, inherited and acquired. Tumors of the brain; their origin in early life; early diagnosis. Studies as to the value of various diagnostic methods. Ventriculography; encephalography; neurosurgical treatment.

II. *Investigation of the Neuroses and Psychoses of Early Life.* This includes:

(*a*) Factual studies relative to hysteria and to the various choreas, tics, minor neuroses and minor mental peculiarities.

(*b*) Studies on problems of behavior and adjustment, with a consideration of normal behavior.

(*c*) Studies on: Normal psychology; recognition of the first signs of psychoses; dementia praecox; the manic-depressive psychosis; paranoid conditions; syphilitic and other forms of early mental disease; juvenile dementia paralytica.

III. *Investigation of Social, Personality and Home Problems.* These include: the development of character, personality studies, proper home training, the place of the child in the family, the parent-child and the teacher-child relationship, educational methods, the question of social adjustment and the physical and mental condition of the child, especially in relation to truancy, delinquency and crime in early years.

The program outlined is given as a general suggestion of the field now open for advanced research. Many other topics may be suggested by those interested in the health and welfare of children.

The committee can consider only original work that promises to be fruitful of results. The applicant must state distinctly the problem under investigation and the methods to be pursued. After Sept. 10, 1936, communications may be addressed to: Child Neurology Research, Bernard Sachs, M.D., Director, 116 West Fifty-Ninth Street, New York.

ELEVENTH INTERNATIONAL CONGRESS ON PSYCHOLOGY

The Eleventh International Congress on Psychology, to be held in Madrid, originally announced for Sept. 6 to 12, 1936, has been postponed until the end of July 1937. The exact date will be announced later. The postponement has been made in part to permit members who desire to do so to attend the Congress on Mental Hygiene in Paris in July 1937 and the Congress on Philosophy in August 1937. For further information communications should be addressed to the secretary, Dr. José Germain, Instituto Nacional de Psicotecnía, Alberto Aguilera, 25, Madrid, Spain.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

Certificates were granted to the following on May 8 and 9, 1936:

Without Examination.—In Neurology and Psychiatry: Albert C. Buckley, Philadelphia, Pa.; George Kirby Collier, Rochester, N. Y.; Isador H. Coriat, Boston; Delmer Dennis Durgin, Central Islip, N. Y.; John Favill, Chicago; Morgan Brewster Hodskins, Palmer, Mass.; Isidore Margaretten, New York; Howard Russell Masters, Richmond, Va.; Newdigate Moreland Owensby, Atlanta,

Ga.; Clarence Anderson Patten, Philadelphia; Abraham Max Rabiner, Brooklyn; Paul Ferdinand Schilder, New York; George Meade Settle, Baltimore; Andrew Leonard Skoog, Kansas City, Mo.; Joseph Smith, Brooklyn; Irving J. Spear, Baltimore; James Joshua Terrill, Dallas, Texas; Max H. Weinberg, Pittsburgh; Guy Ferguson Witt, Dallas, Texas; William Walter Young, Atlanta, Ga.

In Psychiatry: Arthur Nelson Ball, Northampton, Mass.; Olga Louise Bridgman, San Francisco; Charles Whitfield Castner, Wichita Falls, Texas; Edmund McCollam Connely, New Orleans; Clara S. Eirley, Logansport, Ind.; Elmer Vail Eyman, Philadelphia; George Herman Freeman, St. Peter, Minn.; George Arthur Gaunt, Brookline, Mass.; Gerald Reid Jameison, New York; Abram Kardiner, New York; Charles Ten Eyck La Moure, Mansfield Depot, Conn.; Philip Raphael Lehrman, New York; David M. Levy, New York; George E. McPherson, Belchertown, Mass.; Henry Brown Moyle, Hartford, Conn.; Glenn E. Myers, Los Angeles; Mary Gill Noble, Mattapan, Mass.; Lloyd James Thompson, Durham, N. C.; Walter Lewis Treadway, Washington, D. C.; Harvey Watkins, Polk, Pa.

In Neurology: Roy L. Leak, Middletown, Conn.; Charles Edward Thompson, East Gardner, Mass.; W. Franklin Wood, Waverley, Mass.

With Examination.—In Psychiatry: Forrest Nelson Anderson, Los Angeles; Clarke Horace Barnacle, Denver; Edward G. Billings, Denver; William F. Roth Jr., Franklin, Tenn.; Charles A. Rymer, Denver; James Hardin Wall, White Plains, N. Y.; Clifford Leland Williams, Logansport, Ind.; Paul Ivan Yakovlev, Palmer, Mass.

In Psychiatry and Neurology: Lauretta Bender, New York; Walter L. Bruetsch, Indianapolis; Melbourne John Cooper, San Antonio, Texas; Frank J. Curran, New York; Joseph L. Fetterman, Cleveland; Jacob Ellis Finesinger, Boston; A. Hauser, Houston, Texas; William Malamud, Iowa City; Merrill Moore, Boston; Ira C. Nichols, Providence, R. I.; Theodore A. Watters, New Orleans.

In Neurology: Luman E. Daniels, Denver; Harold Cornelius Voris, Chicago; Mabel Garden Masten, Madison, Wis.

Editorial

TUMOR OF THE BRAIN AND USEFUL SURVIVAL

In regard to operation for tumor of the brain Sir William Gowers wrote in 1893: "The danger is not yet fairly indicated by the published facts." He spoke at a time when the few surgeons who had successfully opened and closed the cranial cavity were still a little awed by their own temerity. Perhaps they hesitated to assess their early results with too critical an eye, fearing, like pioneers in other fields, that if they stopped to look back they might lose heart and never enter the promised land of new surgical endeavor.

Two thousand tumors of the brain, with corresponding histologic preparations, have been transferred from the former services of Dr. Harvey Cushing in the Johns Hopkins Hospital and the Peter Bent Brigham Hospital to the pathologic department of the Yale University School of Medicine. This unique collection, with complete copies of the clinical records and the results of follow-up observation, now forms the basis of a Brain Tumor Registry, under the curatorship of Dr. Louise Eisenhardt. Here it is hoped that it may serve the profession at large as a permanent museum to be referred to and enriched by other workers in the field.

Mr. Hugh Cairns, of the London Hospital, having published a report of all the cases of tumor of the brain in which operation was performed while he was an assistant in Cushing's clinic in the year 1926-1927, has now analyzed the subsequent histories of the patients throughout a period of nine years following their operations in an article entitled "The Ultimate Results of Operations for Intracranial Tumors.[1] The facilities of the Brain Tumor Registry made this study possible.

Cairns, following the example of Van Wagenen,[2] another distinguished former assistant of Cushing, has inquired into the usefulness and happiness of the lives of the 135 patients who left the hospital in the series of 157 persons on whom operation was performed during his year of house service. He referred in the ensuing discussion to

1. Cairns, H.: The Ultimate Results of Operations for Intracranial Tumors, Yale J. Biol. & Med. **8**:421 (May) 1936.

2. Van Wagenen, W. P.: Verified Brain Tumors: End Results of One Hundred and Forty-Nine Cases Eight Years After Operation, J. A. M. A. **102**:1454 (May 5) 1934.

540 tumors of the brain from his own subsequent series of operations. As might be expected, the eventual results in each case were determined to a large extent by the location as well as by the nature of the growth. The best results were obtained in general in cases in which the tumor was located in the frontal or the occipital lobe or in the body of the cerebellum. The least satisfactory results followed removal of tumors from the parietal lobe, suprasellar region and extracerebellar spaces.

From the point of view of prognosis, Cairns subdivides tumors into benign and malignant types, placing under the head of benign tumors pituitary adenoma, encapsulated neoplasms, tumors of the blood vessels, congenital tumors and three types of glioma—cerebellar astrocytoma, ependymoma and spongioblastoma polare. As malignant tumors he describes sarcoma, papilloma, metastatic growths and the following types of glioma: glioblastoma multiforme, cerebral and pontile astrocytoma, medulloblastoma, astroblastoma and oligodendroglioma.

This realinement of the types of glioma may be open to criticism, and yet most surgeons of experience will agree that it has much to recommend it. Astrocytoma in the pons or cerebrum behaves in a much more malignant manner than in the cerebellum. Spongioblastoma polare, in spite of its name, is at times benign, and, on the contrary, oligodendroglioma and astroblastoma, in spite of the higher level of differentiation of the type cell, may behave in a malignant manner.

It appears that the histologic classification proposed on an embryologic basis by Cushing and Bailey may not prove to be permanently satisfactory. However, it is obvious that it has served the essential purpose of analytic study. Long experience with the biologic character of these tumors will determine the survival of the classification.

In addition to the many pleasing results, Cairns points out that after intracapsular extirpation of a neurinoma of the acoustic nerve all the patients continued to have severe disturbance of balance, and most of them were subjected to a second operation in a few years. In fifteen of the twenty-five survivors of extirpation of a supratentorial tumor, epilepsy as a postoperative phenomenon was present in some form, although it was mild in all but three instances. These disturbances are sequelae which only careful follow-up analysis brings to light. They present problems which each surgeon must ponder.

In the last analysis the treatment of disease is a human rather than a scientific problem. A temporary cure may well be a triumph, while the permanent saving of a life may be a failure because of postoperative disability. For example, the removal of a cerebellar medulloblastoma, which recurred in eighteen months, led the father of the little patient

to write after her death: "You have given us a wonderful year and a half. Neither she nor her parents were ever so happy at any time in their lives as since her operation." This was a success as judged by human standards, although not impressive in surgical statistics.

In Cairns' report the demand of Gowers that the danger of operation from brain tumor be published has been fairly answered. Furthermore, the results have been expressed in terms of the happiness and usefulness of the life preserved.

Abstracts from Current Literature

Anatomy and Embryology

Relation of Arteries to Roots of Nerves in Posterior Cranial Fossa in Man. James C. Watt and Angus N. McKillop, Arch. Surg. **30**:336 (Feb.) 1935.

The surgical importance of the relationship of the arteries to the cranial nerve roots of the posterior fossa prompted this study, based on approximately sixty cases. Considerable variability in the origin and course of vessels having close relationship to the nerve roots was noted. The term "trigeminal artery" was suggested for an almost constant branch of the basilar artery which courses laterally across the pons and then on the ventral surface of the sensory root of the trigeminal nerve. The internal auditory artery arises from the anterior inferior cerebellar artery and not from the basilar artery, as stated in the textbooks. The anterior and posterior inferior cerebellar arteries and the internal auditory artery were observed to pass dorsal or ventral to, or to loop around or to pass between, their corresponding closely related nerve roots. Sperling, Los Angeles.

The Metabolism of the Phospholipids: VIII. The Passage of Elaidic Acid into Tissue Phospholipids; Evidence of the Intermediary Rôle of Liver Phospholipid in Fat Metabolism. R. G. Sinclair, J. Biol. Chem. **111**:515, 1935.

Sinclair has attempted to ascertain the rate of turnover of phosphatides by feeding rats a fatty acid which is foreign to the rat's body but which is presumably metabolized, as are palmitic and oleic acids. Elaidic acid, the stereoisomer of oleic acid, was chosen for this purpose. It was found that when this acid was fed to rats it entered into phosphatide molecules as do the more usual fatty acids. The mere entrance of elaidic acid into tissue phosphatides, however, is not sufficient evidence to justify the conclusion that it has done so as a stage in its combustion. To prove that this is true it is necessary to demonstrate: (1) that elaidic acid can replace normal fatty acids in phosphatides of adult rats; (2) that the rate of entrance is a rapid process, and (3) that the elaidic acid disappears from the phosphatides when it is replaced in the diet by natural fats.

It was shown that when rats were fed elaidin (the combination of elaidic acid with glycerol), maximum replacement of the natural fatty acids in the phosphatides of the liver by elaidic acid was complete within one day. Reversal of the process by feeding beef tallow also occurred within a day. All of the postulates were therefore fulfilled, indicating that the formation of phosphatide may be an intermediate stage in the combustion of fatty acids. On the basis of previous work, Sinclair was not of the opinion that this is so. He now suggests that there are two types of phosphatides: one class comprised of the more highly unsaturated phosphatides which may function as essential elements in the composition of cells; another consisting of the less unsaturated phosphatides which function as intermediary products in the metabolism of fatty acids.

Investigations advancing knowledge of phosphatides are of especial interest to those concerned with the metabolism of cerebral tissue. Except for the liver, no other organ contains so much phosphatide as the brain. Page, New York.

Nerve Impulses from Receptors in the Mouth of the Frog. R. J. Pumphrey, J. Cell. & Comp. Physiol. **6**:457 (Aug. 20) 1935.

The impulses in the nerves supplying the superficial epithelium of the mouth of the frog were recorded photographically by means of an amplifier in conjunc-

tion with a Matthews oscillograph. It was shown that there are specific receptors for acid and saline substances and tactile stimuli in the mouth of the frog. Impulses which were provisionally regarded as mediating pain were also recorded.

CHORNYAK, Philadelphia.

COLOR CHANGES IN PALAEMONETES. F. A. BROWN JR., J. Morphol. **57**:317 (June 5) 1935.

The shrimp, Palaemonetes vulgaris, adapts itself to white, yellow, red, green, blue, dark gray and black backgrounds by the mixing and dispersion of red, yellow, blue and white pigments. All except the blue are found exclusively within chromatophores. The blue pigment appears to be in the same cells as the red, but it disperses beyond the confines of the cells and disappears from tissues, seeming to be destroyed in situ. In darkness the red pigment varies from a fully concentrated condition to one of half dispersion; the white pigment is concentrated, and the blue pigment vanishes. Formation and destruction of the pigments as well as migration are therefore involved in color adaptation. The state of dispersion or concentration of each pigment is independent of the state of any other pigment and is determined by the color of the background. The rates of migration of the red and white pigments are about the same, but the rate of concentration is about double the rate of dispersion.

WYMAN, Boston.

ABNORMALITIES IN FLATFISHES (HETEROSOMATA): I. REVERSAL OF SIDES; A COMPARATIVE STUDY OF THE KNOWN DATA. E. W. GUDGER, J. Morphol. **58**:1 (Sept. 5) 1935.

Of flatfishes which lie on one blind and colorless side with the upper side two-eyed and colored, some normally lie right side up (dextral) and others left side up (sinistral). The simplest departure from these normal conditions is reversal; i.e., a normal dextral fish lies on its right side or vice versa. Sixteen reversed fishes have been described, but in various species from 3 to 100 per cent reversals have been noted. From a comparative study of the known data it seems that reversal is not dependent on the structure of the optic chiasma but that its explanation must be found in genetics.

WYMAN, Boston.

THE SLIT SENSE ORGANS OF SPIDERS. BENJAMIN JULIAN KASTON, J. Morphol. **58**:189 (Sept. 5) 1935.

The histologic structure of the slit sense organs was studied in fifteen species of spiders from nine families. These organs are probably the same in all spiders. A compound organ consists of several more or less parallel slits in the exocuticular layer which are separated by thick laminae and are covered by a thin epicuticular membrane. A thinner membrane is present at the inner ends of the slits. The hypodermal portion of the organ consists of tall cells with granular basal and fibrillar distal cytoplasm. There is one typical bipolar neuron for each slit of the organ. The distal sensory fiber traverses the fluid-filled slit and ends at the outer membrane. Single slits are essentially like those of compound organs. They closely resemble the pore-plate organs of Kraepelin (sensilla placodea of Schenk) found on the antennae of insects. The term sensilla tomosa is suggested for them, in accordance with Schenk's nomenclature for insects. It is highly probable that their function is chemoreceptive.

WYMAN, Boston.

THE NEUROMOTOR SYSTEM OF OXYTRICHA. EVERETT E. LUND, J. Morphol. **58**: 257 (Sept. 5) 1935.

The neuromotor system and associated organelles of the fresh water ciliate, Oxytricha, were studied in living specimens under dark-field illumination and in total mounts and histologic sections. The action and probable function of each

type of cirrus were determined in normal, anesthetized and dissected specimens. It was found that the neuromotor system consists of the adoral membranelles and coordinating fibrils, the undulating membrane and its basal fibril, two sets of cytostomal fibrils and two sets of postesophageal fibrils. The motor and feeding organelles, morphologically independent of the neuromotor system, include eight frontal cirri, five ventral cirri and a variable number of marginal cirri. The five anal cirri may join the neuromotor system in the region of the posterior end of the undulating membrane fibril. This could not be conclusively determined. A coordinating center (neuromotorium) was not observed in conjunction with this otherwise complete neuromotor system. WYMAN, Boston.

MEDULLA OF CROTALUS ATROX. FRANCIS J. WARNER, J. Nerv. & Ment. Dis. **81**:504 (May) 1935.

The medulla of the rattlesnake shows fairly small trigeminal nerve roots as compared with the extremely large trigeminal nerve roots in the medulla of reptiles that live in water. The mesencephalic root of the trigeminal nerve is extremely large as compared with that of other serpents. The abducens nucleus is slightly posterior to the entrance of the seventh nerve roots. Its position is probably due to the diminished volume of stimuli of the relatively smaller optic tectum in Crotalus as compared with the larger tectal centers in Varanus. Owing to the legless condition of the rattlesnake, the cerebellum is not of the exverted type. The medial part of the cerebellum has undergone marked hypertrophy, while the lateral lobes, or partes laterales, are very rudimentary. The cochlear nuclei are noticeably smaller than those of Varanus salvator and Alligator sklerops, owing to the fact that the sense of hearing in Crotalus atrox is poor. The vestibular nuclei are also somewhat reduced in size and show a simpler nuclear grouping. As in all reptiles, the glossopharyngeal motor nucleus and its motor nerve root are relatively small and difficult to identify. The spinal nerve root and nucleus of the accessory nerve are not to be found in Crotalus. HART, Greenwich, Conn.

Physiology and Biochemistry

STUDIES ON LIPOIDS AND LIPOID DISEASES: IV. LIPOID CONTENT OF TISSUES IN CASES OF STATUS EPILEPTICUS, TOXIC ENCEPHALOPATHY AND CHRONIC LEPTOMENINGITIS. MURRAY COWIE and M. CATHARINE MAGEE, Am. J. Dis. Child. **49**:884 (April) 1935.

Cowie and Magee have studied the total lipoid, the cholesterol and the phospholipoid content of the various tissues in children of different ages dying in status epilepticus. They also recorded the same findings in cases of acute encephalopathy, chronic leptomeningitis, severe anemia and Schüller-Christian's disease. The phospholipoid-cholesterol ratio in cases of status epilepticus varies from 6.2:1 in the lungs to 17:1 in voluntary muscle, whereas in cases of other conditions the average ranged from 5.1:1 in the lungs to 6.5:1 in the liver and 5.8:1 in muscle. It was considered from these conclusions that the phospholipoid-cholesterol ratio in cases of epilepsy during status epilepticus is definitely higher than in other cases which were observed, and these observations are said to supplement those on the plasma of epileptic patients. WAGGONER, Ann Arbor, Mich.

THE SENSE OF SMELL. CHARLES A. ELSBERG and others, Bull. Neurol. Inst. New York **4**:1, 1935.

I. *A New and Simple Method of Quantitative Olfactometry* (Charles A. Elsberg and Irwin Levy).—Elsberg and his co-workers have undertaken a number of clinicophysiologic studies on the sense of smell. The first article deals with the description of a relatively simple device with which quantitative as well as qualitative tests of olfactory sensation can be made. A large number of odorous substances were tested, and their olfactory coefficients were determined. These are

listed in a table. Detailed instructions for the construction and operation of the testing apparatus are given.

II. *A New Principle for the Classification of Odors Based upon Their Olfactory Coefficients* (Charles A. Elsberg, Irwin Levy and Earl D. Brewer).—This article deals with the principle for the classification of odors based on their olfactory coefficients. The authors believe that by the use of the testing apparatus it is possible to establish accurately the olfactory coefficients of odorous substances and to arrange the odors in order according to the numerical values of their olfactory coefficients.

III. *The Relation Between the Olfactory Coefficients and Boiling Points of Odorous Substances* (Charles A. Elsberg, Earl D. Brewer and Irwin Levy).—The third portion of the study is concerned with the relation between the olfactory coefficients and the boiling points of odorous substances. The authors conclude (1) that the olfactory coefficients of odorous substances vary directly as the boiling points; (2) that one molecule of an odorous substance in every hundred molecules of a volatile nonodorous substance raises the boiling point of the mixture by a nearly constant fraction of its value—approximately 0.0105—and (3) that the olfactory coefficients represent either odor pressures or vapor pressures modified by the presence of odor particles.

IV. *Concerning Conditions Which May Temporarily Alter Normal Olfactory Acuity* (Charles A. Elsberg, Earl D. Brewer and Irwin Levy).—The fourth and final portion of the study deals briefly with conditions which temporarily alter normal olfactory acuity. Temporary diminution in olfactory acuity was found in persons during the menstrual period, during and for several weeks after rhinitis and after the ingestion of certain drugs and foods. The authors believe that there are other conditions which temporarily influence the efficiency of the olfactory receptors.

KUBITSCHEK, St. Louis.

THE HISTOCHEMISTRY OF THE HYPOPHYSIS CEREBRI: THE QUANTITATIVE DISTRIBUTION OF VITAMIN C. DAVID GLICK and GERSON R. BISKIND, J. Biol. Chem. **110**:583, 1935.

Glick and Biskind have studied the distribution of vitamin C in the hypophysis by a histochemical method. They found that the ratio of the concentrations of vitamin C in the pars nervosa, the pars intermedia and the pars distalis is about 1:4.7:3. It appears that the pars intermedia is the most potent source of vitamin C yet recorded. The estimated maximum amount of the vitamin in cortical cells of beef adrenal glands is 0.000003 (3×10^{-6}) microgram, while in the pars intermedia it is 0.0000046 (4.6×10^{-6}) microgram. The high concentration of this vitamin in the pituitary gland, which is concerned with the oxidation-reduction reactions in the body, is of great interest, but its significance is unknown.

PAGE, New York.

THE CHANGE OF ALTERNATING CURRENT IMPEDANCE OF MUSCLE PRODUCED BY CONTRACTION. EMIL BOZLER, J. Cell. & Comp. Physiol. **6**:217 (June 20) 1935.

The electrical impedance of the sartorius muscle of the frog during contraction was determined in the hope that it might give further clues as to the nature of the contractile process. The impedance rose simultaneously with the tension. The change of impedance lasted longer than the contraction. An increase of impedance was also observed in muscles in which rigor was produced by iodo-acetic acid, and a decrease was seen in those in which it was produced by chloroform. Although the experiments showed a definite correlation of the change of impedance in muscle with the development of tension, it was not possible to relate them to any known physical or chemical changes which may be responsible for the contractile process.

CHORNYAK, Philadelphia.

CHANGES IN THE EFFICIENCY OF MUSCULAR CONTRACTION UNDER PRESSURE. McKEEN CATTELL, J. Cell. & Comp. Physiol. **6**:277 (June 20) 1935.

Cattell describes experiments in which simultaneous measurements of tension and heat under various degrees of hydrostatic pressure were made on isolated sartorius muscles from the frog. The results indicated a primary stimulation of the energy-yielding mechanism, followed at higher pressures by a depression. At intermediate grades of pressure there was a decrease in efficiency, which suggested that there was some interference with the mechanism concerned in the development of elastic potential, such as would be imposed by an increase in internal friction.

CHORNYAK, Philadelphia.

FRONTAL ASSOCIATION AREAS IN PRIMATES. CARLYLE F. JACOBSEN, J. B. WOLFE and T. A. JACKSON, J. Nerv. & Ment. Dis. **82**:1 (July) 1935.

An experimental analysis of the rôle of the frontal association areas in mediating complex adaptive behavior was undertaken, with monkeys and chimpanzees as the experimental material. Instrumentation, problem boxes, discrimination tests, and delayed response were used for experimentation. The animals were then subjected to lesions of the frontal association areas and of other areas of the cerebral cortex. It was found that after injury to the frontal association areas those activities which demand integration over a period of time can no longer be effectively carried out. The subject seems unable to remember a single experience for even a few seconds in the face of new incoming sensory data, and temporal patterning of responses fails. The memory defect cannot be regarded as a generalized deterioration of intelligent behavior but appears to be a specific impairment of recent memory in the face of normal adjustments to other aspects of the test situations. The present evidence suggests that this is a qualitative rather than a quantitative loss. The basic disturbance is also manifest in the affective reactions.

An "experimental neurosis" was established by continued training on a problem situation too difficult for the animal to master. After bilateral extirpation of the frontal areas the animal no longer had temper tantrums when it made mistakes and continued training on difficult problems did not evoke an "experimental neurosis." On the other hand, behavior suggestive of the Witzelsucht which characterizes similar lesions in human beings was noted. The defect of recent memory cannot be ascribed merely to an extensive injury to the cortex, since lesions to other areas produced minimal, if any, changes; on the contrary, the specificity of the frontal areas for mediating this function is indicated.

HART, Greenwich, Conn.

Neuropathology

CEREBRAL SEQUELAE OF ICTERUS GRAVIS NEONATORUM AND THEIR RELATION TO KERNIKTERUS. H. M. ZIMMERMAN and HERMAN YANNET, Am. J. Dis. Child. **49**:418 (Feb.) 1935.

Zimmerman and Yannet report a case of icterus gravis neonatorum in which recovery occurred during the first month of life, followed by more or less normal development until 5 months of age, when clonic convulsive attacks began; these were followed by and associated with athetoid movements. Progressive loss of vision was noted. The child made no effort to speak or to sit up. There was gradual progression of the disease. During the last year of the child's life the temperature frequently rose as high as 106 F., and during the last five months of life it was between 102 and 106 F. most of the time. During the last two months the child was unable to take much food. Marked dysphagia, frequent regurgitation and edema of the extremities were noted. Death occurred suddenly. Examination of the brain showed a destructive process involving the cells of the caudate nuclei, the putamen on each side, the cornu ammonis, the substantia nigra and the dentate, lateral thalamic and red nuclei. There were no pigmented cells in

the substantia nigra. There was destruction of the cells and of the medullated nerve fibers of the pallidum. The authors state that the histologic and pathologic changes in kernikterus are essentially swelling of the ganglion cells, which progresses to complete cytolysis, the other cells being stained yellow, and pigmentation of the interstitial tissues. It is stated that these are the changes which were found in the case described. The lack of pigmentation in the cerebral ganglion cells is explained on the basis of the relatively long time which elapsed between the onset of the disease and the death of the child. The hyperthermia is explained on the basis of a possible association between it and the degenerative changes in the mamillo-infundibular nucleus of the hypothalamic group. It is suggested that kernikterus may play a part in the pathogenesis of status dysmyelinisatus of the pallidum (Vogt).

WAGGONER, Ann Arbor, Mich.

TUMOR OF THE NEUROMYO-ARTERIAL GLOMUS. VICTOR RAISMAN and LEO MAYER, Arch. Surg. **30**:911 (June) 1935.

Three cases of glomal tumor, the first to be recorded in the American literature, are added to the twenty-six cases previously reported. The glomal tumor is a small, benign, slowly growing tumor usually found beneath the finger-nail. It frequently gives rise to severe pain, aggravated by changes in temperature and pressure. This tumor presents a characteristic microscopic appearance of neurogenic and vascular elements. It arises from the neuromyo-arterial glomus body, a normal structure of the skin, which regulates the blood supply and therefore the temperature of the skin. Excision invariably affords complete cure.

SPERLING, Los Angeles.

A CONFUSIONAL STATE ASSOCIATED WITH INFECTIVE ENDOCARDITIS. DAVID SHAW, Brit. M. J. **1**:1313 (June 29) 1935.

The patient whose case is reported, a woman aged 28, showed a confusional state which was associated with septic endocarditis. During the early stages of the illness she was alert at times. Before death she had periods of extreme drowsiness and confusion and gradually deteriorated. Autopsy demonstrated extensive ulcerative endocarditis with concomitant cardiac changes. The brain contained hemorrhagic areas, particularly in the occipital poles; infarction was widespread. It seems probable to Shaw that the patient's dulled mental state and emotional instability were due to repeated small embolic hemorrhages in the frontal lobes and hemispheres generally, and possibly also in the thalamus. He suggests, too, that the confusional states which sometimes occur in patients with advanced endocarditis might be explained on the basis of repeated embolic hemorrhages in the brain. They are not necessarily large enough or so situated as to cause physical symptoms, but are sufficiently destructive to damage the association paths connecting the higher cerebral centers.

BECK, Buffalo.

AN ATYPICAL FORM OF TUBEROUS SCLEROSIS. R. M. STEWART, Brit. M. J. **2**:60 (July 13) 1935.

An unusual case of tuberous sclerosis is reported. The patient, an intelligent married woman aged 21, had been in perfect health until the day of her death. She suddenly had a violent seizure, during which she died. At autopsy the thymus was found to be persistent and enlarged. The brain contained a number of firm nodules in the substance of the cerebral convolutions, while the kidneys, heart and other organs were normal. Histologically the cerebral tumors were typical of those of tuberous sclerosis.

Cases have previously been reported in which either the intelligence was unimpaired or there were no cutaneous manifestations, but in none, as in this patient, was there absence of all the criteria essential for a clinical diagnosis.

BECK, Buffalo.

THE BRAIN OF THE MENTAL DEFECTIVE: III. THE WIDTH OF THE CONVOLUTIONS IN THE NORMAL AND DEFECTIVE PERSON. W. R. ASHBY and R. M. STEWART, J. Neurol. & Psychopath. **16**:26 (July) 1935.

There is no constant relationship between the complexity of cortical convolutional pattern and intellectual endowment, according to the studies of many authors. In order to determine the convolutional pattern of the person who is mentally defective, Ashby and Stewart have devised a method for measuring the mean convolutional width. This is obtained from the equation $\frac{\text{area examined}}{\text{total length of sulci in the area}}$, the mean width varying inversely with the convolutional complexity. Definite areas of the cerebrum were thus measured in sixty-two brains, fifty-four being from defective persons of known mental age and eight being from normal adults. The experimental error of the method was calculated to be sufficiently small to be discounted. The results obtained were contrary to the accepted view. It was found that there is a tendency for the convolutions to be a little narrower than usual in the mentally defective persons and that even this tendency disappears when the width in relation to the size of the cerebrum is estimated. The outstanding characteristic of the convolutions of the brain in the defective person is a wider variety within the group as compared with the convolutions in normal persons.

N. MALAMUD, Ann Arbor, Mich.

THE MYONEURAL JUNCTION OR MOTOR END-PLATE UNDER NORMAL AND SOME PATHOLOGIC CONDITIONS. R. NOËL and B. POMMÉ, Ann. d'anat. path. **12**: 621, 1935.

The theory is advanced that the motor end-plate is not a part of the sarcolemma but is a peripheral type of neuroglial structureless sheath of Schwann in which the finest ramifications of the peripheral nerve fibers disappear. With Régaud's staining method followed by the use of the iron hematoxylin stain, one is able to demonstrate in the sole plate chondriosomes surrounding the clear nuclei and within the granular substance numerous chondriocontes. The latter resemble the gliosomes described by Collin and are easily differentiated from the sarcosomes. Noël and Pommé suggest for these chondriocontes the name *télosomes*. They are siderophilous and therefore stand out by their black color in these preparations. Under certain pathologic conditions changes of these mitochondria have been observed either without or with changes of the muscle fiber. In the first group is described a case of postdiphtheritic polyneuritis. The chronaxia values in this case were higher than normal and the amount of potassium in the gastrocnemius muscle was diminished. Histologic examination showed normal muscle fibers, but there was marked irregularity in the staining qualities of the *télosomes*. In places these were reduced in number with the formation of larger plaques of clogged chondriocontes staining intensely black. The preponderance of such black or yellow siderophilous plaques was evident also in a case of postencephalitic parkinsonism and in a case of disseminated sclerosis. In both cases the muscle fibers were normal, and the amount of potassium was unchanged.

A different histologic picture of the motor end-plate was seen in cases of progressive spinal muscular atrophy. In such a case the atrophic biceps muscle revealed shrunken and irregularly shaped nuclei in the motor end-plate. The *télosomes* were diminished in number, and numerous coarse yellow-staining granules were seen instead of the normal fine black-staining chondriocontes. In a case of paralysis occurring after serum sickness there was a marked diminution of the mitochondria of the end-plate with the formation of coarse granules of different staining qualities. In some motor end-plates the *télosomes* had almost completely disappeared. There was a marked reduction in the amount of the intramuscular potassium and necrosis of the muscle fibers.

WEIL, Chicago.

DISTURBANCES OF CIRCULATION IN THE BRAIN: A CLINICAL AND PATHOLOGICO-ANATOMIC STUDY. F. HILLER, Arch. f. Psychiat. **103**:1 (Feb.) 1935.

Hiller reports an intensive study of fifty-nine cases of apoplectic insults, with an analysis of the clinical features and the pathologic changes. The apoplectic insults fall into three groups: (1) so-called anemic infarcts and areas of hemorrhagic softenings, both of which are undoubtedly due to emboli; (2) arteriosclerotic lesions of the nature described by Marie under the designation of status lacunaris, which are probably due to interference with the nutrition of these areas on the basis of arteriosclerotic vascular disease, and (3) massive hemorrhages in the brain. In fifteen of the cases the insults were of the first group, in sixteen of the second group and in twenty-eight of the third group. Clinically, the first group is characterized by a sudden onset, usually in the daytime and frequently with loss of consciousness, with signs of general circulatory disturbances in the brain, absence of signs of severe sclerosis of the cerebral vessels and symptoms referable to cardiac disturbances, especially valvular. The second group is characterized clinically by general symptoms both mental and physical, referable to arteriosclerosis. There are also cardiac pathologic changes of the arteriosclerotic type, mostly in the coronary arteries in a number of cases. The third group is characterized by very high blood pressure (average, 200 systolic and 100 diastolic) of the essential hypertension type, either sudden or gradual in onset in the daytime and with unconsciousness, in relatively young patients who have previously complained of cerebral symptoms.

Hiller concludes that massive hemorrhages undoubtedly originate in repeated small hemorrhages into the abnormally dilated adventitial spaces of the larger vessels on the basis of pathologic periarterial defects. These are usually caused by disease of the vessels, chiefly arteriosclerotic. This disease of the walls of the blood vessels usually takes place in certain regions of the brain for which it has a certain predilection. Given such a condition, the increased blood pressure finds its outlet by breaking through the pathologic points in these vessels.

MALAMUD, Iowa City.

AN ANATOMICOCLINICAL STUDY OF A CASE OF APRAXIA. G. MARINESCU, M. NICOLESCO and D. GRIGORESCU, Ztschr. f. d. ges. Neurol. u. Psychiat. **151**:559 (Dec.) 1934.

A case of apraxia with motor as well as ideational components is described in a man aged 54, who was left handed. The patient had a global type of apraxia. Reflex acts were normal. There was left hemiplegia of long standing. Spontaneous movements on the right side were preserved. Necropsy revealed a large area of softening in the region supplied by the left middle cerebral artery involving especially the supramarginal gyrus and the parietal lobe. There were other smaller lesions.

MICHAELS, Boston.

LEPTOMENINGEAL CYSTS IN THE REGION OF THE SYLVIAN FISSURE WITH MARKED COMPRESSION OF THE BRAIN SUBSTANCE. EUGENE SCHERER, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:787 (May) 1935.

Scherer reports three cases of a large meningeal cyst causing marked compression of the brain in an older person who died without clinical evidence of disease of the nervous system. The first case was that of a woman, aged 50, who died of heart failure with mitral stenosis. The second case was that of a man, aged 63, who succumbed to a carcinoma of the ileum, and the last case was that of a man, aged 64, who died of heart failure.

In each case there was a large cyst in the region of the sylvian fissure, deforming the brain. In the last two cases the cyst also extended along the base of the brain. The cysts were apparently closed off from the meningeal spaces. There was no gross evidence of disease of the brain except for the deformity due to compression. There were no developmental defects. The cyst extended along the frontal lobe in the first case, along the base of the frontal and temporal lobes in

the second case, and along the base of the temporal and frontal lobes up toward the convexity of the brain and almost to the frontal tip in the third case. The meninges in the neighborhood of the cyst were somewhat thickened.

Histologic examination did not reveal any evidence of inflammation. The outer wall of the cyst was merely thickened arachnoid covered by many endothelial cells. The pia formed the inner wall of the cyst. There were adhesions between the arachnoid and the pia at the edges of the cyst. The brain itself showed few histologic changes. There were definite marginal gliosis and a mild diffuse increase of astrocytes in the white matter. These changes were considered to be a reaction of the brain to compression. There were no ganglion cell changes and no alterations in the white matter. These histologic changes were somewhat more pronounced in the third case because of the unusual size of the cyst.

In the last two cases deformities of the skull were noted in the region of the cyst. In the second case a widening of the middle fossa on the right was noted, and in the third case there was a bulging of the roof of the skull just over the site of the cyst. Scherer explains these bony changes by assuming that the cysts probably began early in life, before ossification of the bones of the skull was complete. He offers no suggestions regarding the pathogenesis of the cysts. There was no history of trauma in any case and no evidence of inflammation. He denies that this meningeal process is a malformation. Study of the history of the patients did not throw any light on the nature of this process.

The absence of all signs or symptoms of intracranial disease with such large cysts is noteworthy. The author was able to find reports of only two similar cases (Kleblesberg, 1913; Schranz, 1933).

SAVITSKY, New York.

Psychiatry and Psychopathology

FAMILY CARE OF MENTAL PATIENTS. HORATIO POLLOCK, Am. J. Psychiat. **91:** 331 (Sept.) 1934.

The present annual rate of increase in the admission of patients to state hospitals is so great that there is a constant need for building newer and larger institutions. Instead of doing this, it should be possible to house many of the patients in private families. Undisturbed and tractable patients, capable of following instructions, constitute about a third of the institutionalized insane persons. Certain classes could not be housed in private families. Particularly excluded from this type of care are noisy, destructive, violent, suicidal, contentious, convulsive, erotic or bedridden patients. Families in the country with large homes can take five or six patients and thus operate a miniature nursing home. Smaller homes could be used for housing single patients. It should be possible to obtain families to take these patients at from $5 to $7 a week. Since it costs the state about $12 per capita a week to maintain these patients, the saving would be considerable. In New York, for instance, if a third of 69,000 institutionalized mentally ill persons could be thus accommodated the saving would be over $100,000 a week, or more than $5,000,000 a year. Community houses should be established at convenient centers. These would serve a triple purpose. They would function as social and recreational centers for the patients; they would provide a half-way house in which the patient could adjust to the community on his way out to the family, and they would function as administrative and medical centers for the group of patients under their supervision.

DAVIDSON, Newark, N. J.

PSYCHOSIS ASSOCIATED WITH THE ADMINISTRATION OF TRYPARSAMIDE. EMIL HOVERSON, Am. J. Syph. & Neurol. **19:**217 (April) 1935.

Reviewing the protocols of 200 patients who had received tryparsamide, Hoverson finds 6 instances of toxic psychosis ascribable to the drug itself. In this series psychosis was a more common complication than visual changes, for only 4 patients showed any untoward effects in the eye or in the optic apparatus. All 6 of the patients who exhibited psychoses were males. In each case the psychotic

exacerbation occurred during the course of treatment with tryparsamide and vanished when treatment was discontinued. In 2 patients the psychosis began after the third injection, in 3 after the fourth injection and in the remaining one after the fifth injection. In each case the onset was abrupt, and the mental symptoms were those of a delirium. The excitement, panic, fearfulness, hallucinations and confusion appear more or less suddenly and are different from the basic psychosis, so that diagnosis is not difficult. In each case recovery from the toxic psychosis promptly followed cessation of the use of tryparsamide. Because of the benign nature of this complication, Hoverson does not consider it a contraindication to the use of the drug.

DAVIDSON, Newark, N. J.

BRONCHIAL ASTHMA AS A NEUROTIC SYMPTOM. ARTHUR HOLUB, Internat. J. Individ. Psychol. **1**:18 (April) 1935.

In many cases of asthma which defies diagnosis or treatment the condition fails to conform to the usual allergic pattern because of a neurotic basis. In these instances one often sees asthmatic attacks occurring at definite, usually emotionally significant, times. Five cases of psychogenic asthma are cited. In all, the paroxysms served to give the patient a feeling of security because they aroused affectionate attention. The attacks made the patient the emotional center of the household, permitting him to dominate, thus affording an outlet for an inherent drive toward power. In all of the cases here reported more or less permanent relief was afforded by psychotherapy along adlerian lines. The patients were taught to avoid evading or retreating from life's problems, to live without the need for reassurance from loved ones and to renounce their insistence on occupying a central position in the family framework.

DAVIDSON, Newark, N. J.

STUPIDITY AS EXEMPTION. IDA LOWY, Internat. J. Individ. Psychol. **1**:102 (April) 1935.

When for any reason the adult members of a family assume that a normal child is stupid, the child is likely to accept their evaluation of his intelligence. This springs in part from the intensification of a feeling of inferiority and in part from an actual desire to escape the responsibilities which belong to the normal child. Lowy cites two cases, those of a boy aged 14 and a girl aged 11. In each case the child had been repeatedly accused of being stupid and was accordingly shy and unaggressive. The boy lived in active fear of various "bogies," isolated and lonesome. The girl remained timidly in the background of school or home, apparently miserably content to accept her inferior status. In each case it was possible to rehabilitate the patient's personality, so that a normal child resulted. The technic consisted of setting before the child tasks easy enough for ready accomplishment, of praising each success, of assuming that the child was normal and of gradually increasing the complexity and difficulty of the task until the child found itself solving difficult problems.

DAVIDSON, Newark, N. J.

BROMIDE PERMEABILITY TEST IN SCHIZOPHRENIA. H. T. CARMICHAEL, J. C. RHEINGOLD and F. E. LINDER, J. Nerv. & Ment. Dis. **82**:125, 1935.

Results of recent investigations give the impression that in persons with schizophrenia there is a tendency to decreased permeability of the blood-spinal fluid barrier and that in persons with psychoses associated with organic changes in the central nervous system the opposite tendency is shown. The authors undertook an analysis of 135 determinations on twenty male patients from 17 to 47 years of age who were free from detectable physical disease or deformity. No study was made of normal controls. Malamud's figures of from 2.8 to 3.2 were accepted as the normal range for the permeability quotient. Hauptmann's modification of Walter's bromide method was employed. The test was repeated once on forty-three patients and twice on twelve patients. No relationship was found between changes in the permeability quotient and changes in the clinical psychiatric

state, the severity of the psychosis, behavior in the ward or the length of the stay in the hospital. A slight positive relationship between age and the permeability quotient was noted. The authors found a considerable variation in the values of the permeability quotient on repeated tests in schizophrenic patients without any corresponding change in the clinical psychiatric state.

HART, Greenwich, Conn.

FUNCTIONS OF PSYCHIATRY IN A TRAINING SCHOOL FOR JUVENILE DELINQUENTS. CLARENCE O. CHENEY, Psychiatric Quart. **8**:439 (July) 1934.

Many of the factors which precipitate personality disorders are also operative in the bringing about of crime and delinquency. The administration of institutions for delinquents and criminals should be in the hands of persons with psychiatric training or in the hands of officials sympathetic to and cooperative with a psychiatric point of view. It is demoralizing to have recommendations of a psychiatric nature blocked or nullified by lay administrators.

In the institution for delinquents, the psychiatrist should examine each newly admitted child and thereby lay the groundwork for a rapport useful in subsequent psychotherapy. The social service department, so valuable an aid in collecting and interpreting the data from which the psychiatrist will have to draw, should be directly under the psychiatrist's supervision. The industrial officers, cottage masters, school teachers and administrative officials should consult with the psychiatrist on the placement, classification and assignment of each inmate. The selection of the personnel of the cottages when changes are made, should be made with the assistance of the psychiatrist. Problems among the officials and within the official family of the institution should be referred to him. The psychiatrist should have much to say in the disciplining of inmates who are not adjusting themselves properly to the institutional regimen. The psychiatrist should be available for individual psychotherapy whenever requests are made for this by the inmate or by an officer. Finally, the advice of the psychiatrist should play a part in the determination of the time of parole and in the supervision of the paroled inmates.

DAVIDSON, Newark, N. J.

PALLIATIVE PSYCHOTHERAPY IN A CASE OF OBSESSIONAL NEUROSIS. WILLIAM J. SPRINGER, Psychiatric Quart. **8**:466 (July) 1934.

Springer reports the reasonably successful psychotherapeutic management of a case of compulsion neurosis in a woman, aged 22, who was suffering from a serious physical deformity because of poliomyelitis. At the age of 18 there developed the fear that passers-by might be looking into her bedroom while she undressed, and she insisted that the shades be pinned down. Physically unable to perform this, she insisted that her mother do it. Afraid that somehow, some masculine glances might have entered the room, she insisted on "wiping" the glances off her clothes before she donned them. She required clean sheets every night, because some man might have touched the bed during the day; then, realizing that men might be employed in the laundry, she demanded that the mother buy new sheets every day. When the mother protested that this was financially impossible, she answered: "Go out and say you bought new sheets." This ritual, which the patient knew was senseless, apparently relieved her sense of guilt. If the mother refused to yield to any of these requests the patient would fly into a temper tantrum; this performance eventually led to hospitalization.

In the author's interpretation, the compulsion served the purpose of gratifying sexual fantasies which the girl knew, because of her deformity, could never be consummated in reality. It also served the purpose of making her dominant in the household. In his approach to the patient, Springer explained to her that she was setting up a private code of morality; that it might not be a wrong code, but that it was an unnecessary one, because her church already had an adequate ethical code which she, as a devout person, should not tamper with. In the hospital she saw under the psychiatrist's direction that her behavior was incon-

veniencing herself and not her family. The realization of this gave a clear motive for getting well. When she attempted to abstain from carrying out her compulsive acts her mind became filled with sexual fantasies. The author encouraged her to indulge freely in these fantasies on the theory that they were better than the compulsive acts. She was able to do this and made progress, showing a decreasing sense of guilt. She was also encouraged overtly to express her hatred of her mother. On her return home she had a serious struggle but slowly returned to something approaching normal mental health, and while not entirely well she is able to get along comfortably in her family, with a few, untroublesome rituals left.

DAVIDSON, Newark, N. J.

OBSERVATIONS ON THE MOTOR PHENOMENA OF HYSTERIA. I. M. ALLEN, J. Neurol. & Psychopath. **16**:1 (July) 1935.

This report is based on a study of fifty-nine cases of hysteria. Disturbances of the motor function are noteworthy for their great variety and complexity and require careful analysis by both physical and psychologic methods. Often light hypnosis may prove useful as it produces a "slow motion" effect of the motor phenomena. The essential effect in the motor system is an inhibition of the motor impulse to the affected muscles, which apparently arises at the unconscious level of the higher cortical functions. The observations confirm the three motor phenomena described by Wilson: (1) contraction of antagonists instead of agonists (most common); (2) contraction of fixation muscles and absence of contraction in simple agonists and antagonists, and (3) complete absence of muscular response. The effects are similar whether they are the result of spontaneous voluntary effort or occur at command or whether they occur in response to a sensory stimulus such as eliciting the plantar reflex. Further effects depend on the presence of the normal stretch reflex in opposing groups of muscles. Local motor phenomena arise as the result of inhibition of agonists, contraction of antagonists, the application of stretch to agonists and contraction of agonists in that order. During recovery, brought about by psychologic means, the hysterical subject passes through phases in which the same sequence is reversed, namely, from complete inhibition to full transmission of the conscious motor impulse. The clinical motor manifestations of hysteria, such as tonic paralysis, tonic paralysis with contractures, tonic paralysis with tremor and minimum tonic paralysis with maximum tremor can be understood in their development only in the light of the aforementioned sequence of the inhibition of the motor impulse. The effect on the tendon and plantar reflexes in selected cases in which no sensory disturbances occur depends on the local muscular condition and the degree of its tonic innervation.

N. MALAMUD, Ann Arbor, Mich.

CONSANGUINITY AND MENTAL DISEASE. MAURICE DESRUELLES and PIERRE GARDIEN, Ann. méd.-psychol. **93**:168 (July) 1935.

When mental disease occurs in a patient born of a consanguineous union there is a tendency to consider the blood relationship as a predisposing factor. It is based mainly on an old lay prejudice, springing from an ethnic taboo, rather than on scientific observations. The matter has been the subject of lively debate in France since 1913. To arrive at a rationally established conclusion, it would be necessary to examine the ratio of consanguineous to nonconsanguineous or crossed marriages among the parents of persons suffering from mental disease. Since this would be complicated by syphilis and alcoholism, such a study would be almost impossible as a means of determining the issue at question. Moreover, it has been shown by August Voisin in a study of a limited area (the island of Batz) where consanguineous marriages are numerous that the descendants are normal if the parents have been sane and if the ascendants have been normal for several generations. Thus, Voisin claimed that consanguinity per se is not an unfavorable influence on mental health.

Opinion has varied from the middle of the nineteenth century to the present and is divided rather sharply into three periods: 1. Before 1859 a unanimous

opinion prevailed. Esquirol, Ellis, Prosper Lucas and most of their contemporaries were of the opinion that consanguineous parents, ipso facto, produced mentally defective or prepsychotic children. The conception was accepted in religious, legal, literary and medical circles. Scientific men were inescapably influenced by the weight of popular prevailing ideas. No writers denied the morbid influence of consanguinity, but Pinel and a few others did not include it in the etiology of mental disease. 2. From 1859 to 1900 ardent controversy reigned. Notably August Voisin, Bertillon, Charcot and George Darwin asserted that the offspring of sane consanguines could be normal; Binet and others favored the opposite view, while Falret, Ribot and Kraepelin withheld opinion. At the beginning of this period the partisan groups were of equal size, but toward the end of the century the innocuity of consanguinity rose in favor. 3. Since 1900 writers on the subject have been almost unanimous in supporting the innocuity of consanguineous marriages of sane parents.

The importance of distinguishing sane from morbid heredity is obvious.

MOORE, Boston.

THE FEELING OF SUFFERED INJUSTICE IN CRIMINAL PATHOLOGY. E. DE GREEFF, Ann. méd.-psychol. **93**:361, 1935.

The exaggerated feeling of suffered injustice is considered by de Greeff to be pathognomonic of certain prodromal states of psychoses, which are especially important because of their criminologic implications. While in normal persons this feeling does not lead to a demand for an equivalent reparation and quickly decreases in strength with the passage of time, in persons with psychasthenia and in those with latent paranoia its development takes a different course. The exaggerated sensitivity of the person with psychasthenia toward every disturbance of the sympathetic atmosphere necessary for his equilibrium makes him measure his hostility to the environment by the intensity of his own suffering. When the limit of tolerance is reached, he may react by an act of violence. The person with paranoia, on the other hand, when he first begins to sense injustice in others becomes especially watchful of himself and frequently develops an excessive honesty and fairness. These qualities, however, though they may procure the patient an excellent reputation, endanger rather than promote friendly relations with persons of his environment, from whom equal fairness is expected. Since the extinction of the emotional processes sets in early, the offenses, unpardoned, are registered purely intellectually, and retaliation becomes a matter of an abstract principle of justice. With actual beginning of delusion formation the patient becomes less dangerous since the satisfaction he obtains from the imaginary retaliation makes it unnecessary for him to act in reality.

MOORE, Boston.

FROM MIMICRY TO LANGUAGE. J. MORLAAS, Encéphale **30**:197, 1935.

Morlaas traces the historical evolution of language from the primitive stage of mimicry, in which an object is designated in speech by its characteristic gesture ("flying" for bird, "swimming" for fish, etc.) and in writing by a pictograph (mimographism) to the present stage of Western languages. The latter have been liberated from the bonds of mimicry by being algebrized (in the phrase of Marcel Jousse). The substitution for the *mimème* of the impersonal, easily handled *algébrème* has made possible the translation of reality into formulas. Simultaneously, certain motor parts of language and thought have been suppressed. Thus, memorization was originally a global phenomenon, putting into action all the "spontaneities" of man. The primitive teacher or narrator sways back and forth as he recites. So do his hearers and so do young children when learning to spell. The modern teacher, however, has "frozen" himself into immobility. Jousse found in the biblical and Homeric rhythms a surprising relationship to the "bodily and vocal explosions of the illiterate old women of the Sarthe." The anthropologic investigations of Jousse corroborate and amplify Pierre Marie's thesis that the language centers are not innate.

LIBER, New York.

Diseases of the Brain

TRAUMA AND THE NERVOUS SYSTEM WITH ESPECIAL REFERENCE TO HEAD INJURIES AND CLASSIFICATION OF POSTTRAUMATIC SYNDROMES (ANALYSIS OF ONE HUNDRED CASES). I. S. WECHSLER, J. A. M. A. **104**:519 (Feb. 16) 1935.

Wechsler states that there are so many pitfalls in the proper evaluation of signs and symptoms following trauma to the head that it is often difficult to arrive at a conclusion or to express an opinion with definite assurance. This holds true to some extent in cases in which there is definite evidence of injury to the brain, but it is particularly true in those cases in which there are manifestations of subjective syndromes. Trauma to the head is fraught with grave possibilities and serious consequences, and prolonged unconsciousness, even in the absence of fracture of the skull or of objective signs of injury to the brain, may be followed by incapacitating sequels lasting months and years. However, with few exceptions, signs of injury to the nervous system set in immediately or within a few hours, or more rarely within a few days, after the accident. Mental symptoms, particularly headache and dizziness, may set in later, and convulsions may appear months or years after the receipt of trauma to the head. Generally, the longer the interval the more difficult it is to establish a causal relationship between trauma and its alleged sequels. In rare instances the already existing pathologic changes of dementia paralytica, alcoholism and the convulsive state may be aggravated by trauma, but they may also be responsible both for the accident and for the injury. It is essential to determine the exact amount of injury to the brain and the degree of psychic coloration of symptoms that are present. In doubtful cases encephalography is of diagnostic help. As this procedure is always unpleasant and occasionally not without dangers, it should be resorted to only as a last measure and with due discrimination. Clinically, it is not easy to differentiate the subjective complaints which follow trauma to the head. Every case, therefore, requires not only a special evaluation of signs and symptoms but also a study of the personality. In view of the existing differences of opinion, of the lack of knowledge and agreement as to the nature of the underlying pathologic changes and of the confusion in terminology, a tentative classification of posttraumatic syndromes is suggested, and the criteria for their recognition are discussed. The syndromes are: malingering, traumatic hysteria, traumatic encephalopathy or concussion and traumatic neurosis. EDITOR'S ABSTRACT.

CHRONIC SUBDURAL HEMATOMA. FRANCIS C. GRANT, J. A. M. A. **105**:845 (Sept. 14) 1935.

Grant bases his report on sixteen cases of chronic subdural hemorrhage in which the diagnosis was verified at operation or at necropsy. In none of them was an accompanying contusion or laceration of the brain the cause of the hemorrhage. There seemed to be an internal as well as an external limiting membrane enclosing a chocolate-colored clot and brownish fluid. The diagnosis in these cases depends on how recent and how cleancut the history of the injury may be. If the clinical picture develops as a direct consequence of cranial trauma, a definite conclusion that a subdural hematoma has formed may often easily be reached. But again the trauma may have been so mild that to attribute to it the development of such marked symptoms after so long a period seems ridiculous. In the present series five patients were never unconscious at any time and five lost consciousness only momentarily, while none of the remaining six were unconscious for more than ten minutes. The importance, therefore, of any injury, no matter how trivial, particularly if violence has occurred in the anteroposterior plane of the head, should be stressed. In six cases the neurologic signs pointed to involvement of the opposite pole of the brain to that actually involved. In other words, the hemorrhage and the hemiparesis were on the same side. On three occasions the hemorrhage was bilateral. Therefore, both hemispheres should always be explored. The proper treatment for chronic subdural hemorrhage is exposure and removal

of the clot. Six patients were operated on through an osteoplastic flap, with no fatal results. In one instance bilateral subtemporal decompression was carried out, recovery resulting. In the eight cases in which simple trephination and evacuation of the clot were employed, four patients recovered and four died. In but one case could the fatal outcome be blamed on the method used. In this case the clot was more solid than fluid. A drain should be left within the dura for from twenty-four to forty-eight hours. The increased bleeding following an osteoplastic flap and removal of the clot occurs mostly from the dura. If the dura is cut all the way round, turned over and resutured, all oozing from its surface will promptly cease. The osteoplastic flap affords room for decompression.

EDITOR'S ABSTRACT.

LOCALIZED NON-SUPPURATIVE ENCEPHALITIS OF OTITIC ORIGIN. J. B. HORGAN, Brit. M. J. **2**:161 (July 27) 1935.

A brief report is submitted of a case which further substantiates the observation by Symonds that localized nonsuppurative encephalitis constitutes a distinct intracranial complication of otitis media. A boy, aged 16, who had suffered from suppurative otitis media on the right side since childhood, showed signs and symptoms resembling abscess of the brain. Complete left hemiplegia with increasing signs of meningeal irritation developed. There was no improvement after a radical mastoidectomy. Later the cerebellum and cerebrum were explored, but the brain substance was entirely free from abscess. The spinal fluid was normal, except that it was under moderate pressure. During the ensuing month the patient made a complete recovery.

BECK, Buffalo.

MENINGOBLASTOMA OF THE LESSER WING OF THE SPHENOID. C. WESKAMP, Ann. d'ocul. **171**:579 (July) 1934.

Weskamp reports a case of meningoblastoma of the lesser wing of the sphenoid. A patient aged 53 had suffered from exophthalmos of the left eye for several years. A photograph taken in 1923 showed that exophthalmos was present at that time, but it had not been noticed by the patient. Vision in the left eye was greatly reduced. He had suffered no pain during the past ten years, but during this period he lost vision completely in the left eye. Exophthalmos measured by Hertel's instrument was 16 in the right eye and 28 in the left eye. It was unaffected by a change in position or by exertion.

Weskamp stresses the fact that not only the eyeball but the entire orbit was exophthalmic. Pulsations, collateral circulation, alteration in the color of the skin and edema were not present. The sensitivity of the skin, conjunctiva and cornea was normal. Although the eyeballs were not parallel, it could not be determined which eye was higher since the left eye turned less than the right. The left pupil was dilated and did not react to light. The other cranial nerves were normal.

Ophthalmoscopic examination of the left eye revealed simple atrophy of the optic nerve, fine arteries and large and slightly sinuous veins. The right eye was normal ophthalmoscopically. An exploratory puncture of the left orbit was made, but no fluid was found. Roentgenographic study revealed generalized hyperostosis of the lesser wing of the sphenoid and of the adjacent portion of the orbital surface of the left frontal bone. The sphenoid fissure was cloudy, especially along the superior border. The great wing of the sphenoid on the side adjacent to the fissure had a similar appearance. The left optic foramen, compared with the right, was markedly reduced in diameter and irregular in outline. The right orbital region was of normal appearance. A meningioma was revealed at operation. It was removed in part. The syndrome of exophthalmos and loss of vision, the roentgenographic picture and the preceding data indicate a tumor of the lesser wing of the sphenoid.

BERENS, New York.

OCULAR SYMPTOMS IN MENINGIOMAS OF THE LESSER WING OF THE SPHENOID. M. DAVID and E. HARTMANN, Ann. d'ocul. **172**:177 (March) 1935.

This article is a summary of observations made by David and Hartmann in the study of twenty-six patients suffering from meningioma of the lesser wing of the sphenoid. The diagnosis was verified histologically in all cases. Ocular disturbances are the principal symptoms of meningioma of the lesser wing of the sphenoid because of their frequency, their precocity and the special characteristics which they show in certain cases. Ocular symptoms are generally present; their absence is exceptional. David and Hartmann noted the absence of ocular symptoms only once in the twenty-six patients observed. In six cases, approximately 25 per cent, ocular disturbances were the principal findings. Lesions in the fundus oculi were present in twenty-four cases (92 per cent). They were distributed in the following manner: bilateral papilledema, fourteen cases, or 54 per cent; bilateral atrophy of the optic nerve with veiled margins of the disks, three cases, or 11 per cent; primary atrophy of the optic nerve on one side and atrophy with veiled borders of the disk on the other side, one case, or 4 per cent, and the Foster Kennedy syndrome, six cases, or 23 per cent. The fundus was normal in two cases, or 8 per cent.

BERENS, New York.

AN ISOLATED CASE OF CRANIOFACIAL DYSOSTOSIS (CROUZON). A. VAN LINT, L. VAN BOGAERT and R. THIENPONT, J. belge de neurol. et de psychiat. **35**:65 (Feb.) 1935.

Van Lint, van Bogaert and Thienpont present the case of a boy aged 11, the only child of healthy parents. He was born at term; delivery was easy, and he appeared normal at birth. He was fed by breast for four months. At 6 months the parents noticed progressive bilateral exophthalmos and a change in the shape of the skull. At 1 year a mass began to form in the region of the anterior fontanel, and vision appeared to be poor. These symptoms increased until the age of 7 years, from which time they appeared to be stationary. On examination there was a mass the size of an orange in the region of the anterior fontanel. It was hard, somewhat elongated and without pulsation. The skull was strongly brachycephalic, with widening of the parietotemporal region. A description of the face is characteristic. There was projection of the mandible, the upper lip was thin, the nasolabial groove was very marked and there was a parrot-like nose, the base of which was extended and prolonged into the superciliary ridges. There was marked exophthalmos, with an associated marked divergent strabismus. The neck was short and the thorax small. There were no symptoms of rickets. The rest of the body was more or less normal. Ocular examination showed that the patient could count fingers at 10 cm. There was myopia of 2 diopters, with astigmatism. There were slight horizontal nystagmus and atrophy of the optic nerve. Laboratory examinations gave negative results.

The differential diagnosis lay between craniofacial dysostosis and oxycephaly, the important points in favor of the former being the facial aspect, the exophthalmos with divergent strabismus and the date of appearance of the deformities. The etiology and pathogenesis of the condition are unknown; presumably it is a hereditary anomaly. No definite hereditary taint was found in the patient's family history.

WAGGONER, Ann Arbor, Mich.

HYPERTELORISM OF GREIG (SPORADIC AND HEREDITARY TYPE). LUDO VAN BOGAERT and JACQUES SWEERTS, J. belge de neurol. et de psychiat. **35**:71 (Feb.) 1935.

Hypertelorism is associated with a craniofacial congenital deformation, which consists essentially of abnormal separation of the orbits. The nasal bridge is large, and the bones which comprise it are hypertrophied. There may be in addition a reduction in the height of the frontal bone and a flattening of the occipital bone. Cases of the complete form are rare. Cases of the mild type are rather frequent. The two cases reported in this article are the eleventh and twelfth to

be reported in the literature. Apparently this condition is frequently associated with other extraneural anomalies. Some patients suffer from convulsive attacks and mental retardation.

WAGGONER, Ann Arbor, Mich.

RETINAL NEURO-ECTODERMOMA IN A CASE OF RECKLINGHAUSEN'S NEUROFIBROMATOSIS. H. ROGER, J. ALLIEZ and J. PAILLAS, Rev. d'oto-neuro-opht. **13**: 365 (May) 1935.

The multiple and curious manifestations of the neurogliomatosis of Recklinghausen are well known. Recently attention has been directed to the occurrence of retinal tumors of slow growth in the course of Recklinghausen's disease, and analogous manifestations have been seen in tuberous sclerosis and in Lindau's disease. Van der Hoeve grouped these three diseases under the name of phacomatosis and insisted on the importance of their ocular signs. In tuberous sclerosis flat tumors with incrustations are found in the retina. They may become cystic and are made up of neurofibrils and large cells with abundant protoplasm, which are regarded as neurocytes. In Lindau's disease the presence of retinal cysts or angiomas is essential for diagnosis. Histologically, besides the cystic degeneration, neighboring zones of angiomatous and proliferating glial tissue are found. In the course of Recklinghausen's disease, van der Hoeve and Niewanhuyse observed retinal tumors and bilateral tumors of the optic nerve. They found tumors analogous to those in tuberous sclerosis together with angiomatous formations.

The authors report the case of a woman, aged 64, who was seen twice at intervals of seven years. She suffered with paroxysmal pain in the left lower jaw and left hemiparesis. A rounded benign tumor next to the papilla was observed. Numerous congenital pigmented spots and more recent nevi were found on the skin, which warranted the diagnosis of neurogliomatosis of Recklinghausen. The name "neuro-ectodermoma" was proposed ten years ago by one of the authors for the group of tumors located both in the skin and in the central or peripheral nervous system.

DENNIS, San Diego, Calif.

A CASE OF SCHÜLLER-CHRISTIAN'S DISEASE. J. NORDMANN, P. PAYEUR and R. SACREZ, Rev. d'oto-neuro-opht. **13**:371 (May) 1935.

A youth aged 19, without significant family history, was admitted to the clinic on account of asthenia, impairment of gait, insatiable thirst and polyuria. His weight and stature had always been below normal. Seven months before admission bosses were noted on the vault of the skull, walking became difficult because of pain in both femurs and a slight exophthalmos was observed in the left eye. The chief findings on physical examination were lack of development of secondary sexual characteristics, a leukocyte count of 15,000, lively reflexes in the legs and disturbances of the glossopharyngeal nerves and spinal accessory nerves. The urinary output varied from 7 to 8 liters per day, and the urine contained a trace of albumin. Roentgenograms of the skull revealed many lacunae in the bones, but no thickening. Examination of the eyes showed nothing abnormal except slight clouding of the papillae and exophthalmos. The characteristic triad of the Schüller-Christian syndrome is geographic skull, exophthalmos and diabetes insipidus. The condition is caused by a disturbance of lipoid metabolism, whereby neutral fats are deposited in the tissues, especially in the flat bones.

DENNIS, San Diego, Calif.

REFLEX EPILEPSY. MACDONALD CRITCHLEY, Schweiz. Arch. f. Neurol. u. Psychiat. **35**:256, 1935.

Although in some cases of reflex epilepsy seizures occur only in response to a given stimulus, more often there is an occasional spontaneous seizure. In still other cases the stimulus is not always effective. Spasms, which are usually of focal character, may become generalized, and consciousness may be lost if the

stimulus is too strong or long continued. In a series of illustrative cases of reflex epilepsy cited by Critchley from his own experience and that of his colleagues, as well as from the literature, those in which tactile or auditory stimuli induced seizures were the most numerous. In many instances the exciting agent had to be unexpected in order to be effective. One of a group of patients who had convulsions on hearing music was susceptible to classical music only. In some cases the causative stimulus, whether tactile, auditory or visual, was similar to the aura preceding spontaneous attacks. Instances are given of brief losses of consciousness or even convulsions precipitated by laughter, orgasm, urination, defecation and emotional disturbances. The possibility of an emotional factor in various types of reflex epilepsy is also considered.

Critchley draws an analogy between reflex epilepsy and a highly inflammable substance. It has been shown experimentally that topical applications of strychnine render certain cortical areas unduly sensitive to incoming stimuli. Similarly, appropriate external stimuli in cases of scar or tumor involving the sensory cortex have been known to precipitate convulsions.

DANIELS, Denver.

Vegetative and Endocrine Systems

CHRONIC SUPRARENAL INSUFFICIENCY. MAURICE PACKARD and H. F. WECHSLER, Arch. Int. Med. **54**:18 (July) 1934.

Chronic adrenal insufficiency is distinguished from Addison's disease by the absence of pigmentation and hypotension; polyneuritis and loss of fat occur in cases of chronic adrenal insufficiency and not in cases of Addison's disease. Three cases of chronic adrenal insufficiency are reported. In the first case the patient, a man aged 53, was cachectic and irrational and suffered from bilateral ptosis of the eyelids. The blood pressure was 110 systolic and 70 diastolic. Quadriparesis was marked, and the deep reflexes were absent. The hemoglobin content was 66 per cent, and there was slight albuminuria. The course was downward, with loss of subcutaneous fat, tremors, progressive weakness and death from bronchopneumonia. At autopsy atrophy of the right adrenal gland and degenerative hypertrophy of the left adrenal gland were found. In the second case the patient, a man aged 68, complained of dyspnea, anorexia and pain in the chest; he was undernourished and cyanotic. The blood pressure was 140 systolic and 55 diastolic. Albuminuria was present. The hemoglobin content was 80 per cent. Anorexia, asthenia, loss of subcutaneous fat and tremors increased. At autopsy a carcinoma of the bronchus was noted. Both adrenal capsules were enlarged, and both were filled with carcinomatous tissue. In the third case, the patient, a woman aged 39, complained of weakness, anorexia, stiffness and loss of power in all extremities. Her weight had decreased from 150 to 72 pounds (68 to 33 Kg.) in a year. The blood pressure was 78 systolic and 60 diastolic. On treatment with a proprietary preparation of the cortical hormone and a diet high in vitamin D the patient showed some improvement.

Malnutrition was the apparent etiologic factor in all three cases. In none was pigmentation found. The loss of fat—including both the panniculus adiposus and the internal fat deposits—was a striking feature in each case .

DAVIDSON, Newark, N. J.

HYPOPHYSEAL GONADOTROPIC HORMONES. P. E. SMITH, J. A. M. A. **104**:555 (Feb. 16) 1935.

Smith points out that work on the gonadotropic substance from the hypophysis and from other sources (from urine obtained after ovariectomy or after the menopause) strongly indicates that the principle commonly designated as the gonad-stimulating principle is composed of two principles. One of these, a gametokinetic (follicle-stimulating) principle, has been secured in a fair degree of physiologic

purity by fractionation of the anterior lobe of the hypophysis, and it is also present with little or no contamination with other hormones in the blood and urine after the menopause and ovariectomy. Work with the other principle is somewhat less satisfactory. It appears that the other factor, which may at this time be designated as a "luteinizer," causes luteinization of the ovary. It presumably acts also on the interstitial tissue of the testicles. The present indications are that in the therapy of hypogonadism due to hypophyseal deficiency the administration of one or the other or a proper mixture of these two factors will be required to induce normal gonadal function.

EDITOR'S ABSTRACT.

CASTRATION: THE AMELIORATIVE EFFECTS OF THERAPEUTIC CASTRATION IN HABITUAL SEX OFFENDERS. A. W. HACKFIELD, J. Nerv. & Ment. Dis. **82**:15 (July); 169 (Aug.) 1935.

Hackfield considers a group of twenty-five nonpsychotic male patients, of whom twenty were exhibitionists, two were fetichists and three were homosexual. Twenty-two had been sentenced at least once, and most of them many times. An unfavorable hereditary history was found in fifteen cases. In a similar number the ability to have erections and sexual intercourse for from one to several years after operation was shown. Usually the sex drive diminished gradually. In a few cases the facultas coeundi persisted for ten years after operation. In twelve cases a gain in weight, and a diminution in growth of the beard and of hair on the chest, arms and legs occurred immediately after the operation. All fifteen subjects are alive and mentally alert, showing that castration has no ill effects on the general health of the mature person. The extinction or the diminution of the erotic tension resulted in more steady habits of life and resultant increased working capacity. Cessation of all erotic and perverse dreams occurred in nine cases.

A group of fifteen psychotic patients are contrasted with the foregoing group. Castration had been undertaken with the view to minimizing the abnormal sex drive. In all nine castrated women the operation was unsuccessful. The author states positively that castration has no curative effect in the case of psychotic or otherwise mentally defective sexually abnormal men and sexually promiscuous psychotic or nonpsychotic women. The libido, according to the author, cannot have its seat in the sex glands alone.

HART, Greenwich, Conn.

HYPOPHYSEAL CACHEXIA (SIMMONDS' DISEASE) WITH ATROPHY OF THE ANTERIOR LOBE OF THE PITUITARY GLAND. LEWIS GUNTHER and CYRIL B. COURVILLE, J. Nerv. & Ment. Dis. **82**:40 (July) 1935.

The history and postmortem observations in a case of hypophyseal cachexia (Simmonds' disease) with atrophy of the pars anterior of the hypophysis are described. The appearance of this characteristic symptom complex is most commonly associated with atrophy, with or without sclerosis, of the anterior lobe, the pars nervosa being preserved in most instances. The occurrence of partial or complete atrophy of the hypophysis without this clinical picture makes it evident that there is some other unexplained factor in Simmonds' disease. Other endocrine glands, notably the thyroid, the gonads and the adrenals, are also frequently atrophied. General visceral atrophy is attributed to loss of activity on the part of the eosinophil cells, which is an observation to be contrasted with splanchomegalia or hypereosinophilia.

HART, Greenwich, Conn.

STUDIES IN THE NEUROLOGICAL MECHANISM OF PARATHYROID TETANY. RANYARD WEST, Brain **58**:1, 1935.

Dogs in which tetany was induced by parathyroidectomy were studied for the effects of partial or complete denervation of one hindlimb, of complete transection of the spinal cord in the thoracic region and of interruption of the dorsal roots of one or both hindlimbs. Paton, Findlay and Watson (1916) stated that section

of the nerves to any part entirely and immediately abolishes all tremors and jerkings of the muscle supplied by those nerves. West found that after section of a peripheral nerve clonic and fibrillary tetany can occur in muscles denervated a few hours previously. The latter may occur at least twenty-four hours after denervation. Tonic tetany was not observed. No elements of tetany were observed after the third day. The hyperexcitability to electrical stimuli which occurs in tetany is present to an exaggerated degree for some hours after denervation. A second phase occurs subsequently, in which the electrical reactions of denervated muscle do not fall but tend to rise with the onset of tetany.

After section of the thoracic portion of the spinal cord all three types of tetany occurred: clonic, tonic and fibrillary. The activity of the tetany produced does not appear to be related to the time of occurrence after transection of the cord. It was noted that the activity of the reflexes of the spinal animal tend to increase with the onset of tetany. The myotatic irritability of tetany is retained in the hindlimbs of the spinal preparation. After interruption of the dorsal nerve roots there is great reduction in the activity of tetany. With one temporary exception, the form of tetany in deafferentiated muscles has always been fibrillary. The view that the tetany, both tonic and clonic, is contributed to by sensory impulses is supported by its abolition by deafferentiation.

Fibrillary tetany is tetany in its simplest form and persists if the motor connections between the spinal cord and the muscle remain intact. Thus, with interruption of the peripheral nerve supply after a few days fibrillary tetany does not develop. An intact spinal cord reflex is essential to the development of the tonic and clonic forms of tetany. Thus, with section of the dorsal roots tonic and clonic tetany were not observed, whereas with section of the thoracic portion of the cord all forms of tetany were obtained. It was not found that impulses from higher centers add anything to the pattern of canine tetany.

The essential feature of tetany appears to be the action of a circulatory factor peripherally on some site in the muscle, causing repeated contractions of individual muscle fibers and electrical hyperexcitability. Both this fibrillary tetany and the electrical hyperexcitability are influenced by the nerve supply from the central nervous system.

SALL, Philadelphia.

ULCERATIONS IN THE STOMACH AFTER ADRENALECTOMY. J. FREUD, D. LUWISCH and F. OESTREICHER, Brit. M. J. **1**:1216 (June 15) 1935.

Gastric ulceration has been shown to occur after adrenalectomy in the dog and cat. In man it may follow extirpation of the pituitary gland or hypothalamic lesions. In the light of these findings the mucosa of the alimentary tract was investigated carefully in five dogs in which a two stage adrenalectomy had been performed. All the animals showed defects in the gastric mucosa of varying size and number. The largest varied in diameter from 3 to 7 mm., the depth usually corresponding to the thickness of the mucosa, though sometimes only the superficial layer was dehiscent. The deeper defects resembled classic gastric ulcers. It remains on open question whether the ulceration is primarily due to a hypophyseal or to an adrenal deficiency.

BECK, Buffalo.

A CASE OF CUSHING'S SYNDROME. W. L. BROWN and C. SEWARD, Brit. M. J. **2**:253 (Aug. 10) 1935.

An obese unmarried woman, aged 35, showed the three essential features of Cushing's syndrome: plethoric obesity, hirsuties and amenorrhea. Hypertension, albuminuria, lowered dextrose tolerance and kyphosis, associated with pains in the bones, were also present. Roentgen therapy was given, but the patient could tolerate only 50 per cent of the prescribed dose, as each treatment caused excruciating headache. The condition improved after cessation of treatment.

BECK, Buffalo.

PINK DISEASE. A. JEFFREYS WOOD and IAN WOOD, Brit. M. J. **2**:527 (Sept. 21) 1935.

Pink disease, or infantile acrodynia, is of unknown etiology and occurs in very young children, the majority of them being between 9 and 18 months of age. It attacks male and female children in practically equal numbers. There is no specific pathologic change. The authors have personally studied about 150 cases and divide the symptoms of this disease into three stages, each of the first two stages lasting about one month and the third stage much longer.

The first stage, which is frequently acute, ushers in the illness. This consists of coryza, fever, with the temperature varying from 100 to 102 F., and general malaise. The patient becomes irritable, and sleep is greatly disturbed. There is a complete change in the child's personality; he becomes petulant, obstreperous and extremely miserable. Anorexia soon follows; there are loss of weight and marked muscular weakness. This loss of power is a constant early manifestation, which is very striking if the child is old enough to walk. Toward the end of the first month a sudaminal rash may appear on the trunk and is most prominent during the periods of profuse sweating which so commonly occur. The child begins to avoid the light, owing to photophobia. Itchiness of the face, arms and legs has actually been described by some of the older patients as being intense, and when the younger children are closely observed the great distress produced by this symptom can be fully appreciated. They slowly twist and turn, rubbing and scratching the offending parts either with their hands or against the sides of the bed.

During the second stage the various changes become fully established, and the child presents the classic picture of pink disease. The hands and feet are swollen and either pink or slightly cyanosed, depending on the surrounding temperature. They feel icy cold and the circulation is poor, for if the superficial capillaries are emptied by pressure on the skin the refilling is slow when the pressure is released. Vesicles appear in the skin of the hands and feet which break and then desquamate. Staphylococcic infections frequently appear. Photophobia without apparent conjunctivitis, a rapid pulse rate and often a raised blood pressure, coryza, excessive salivation, severe sweating, a sudaminal rash on the trunk, marked muscular weakness and hypotonia, trophic changes with secondary infections especially in the skin and mouth and invariably a change in the mental attitude complete the distressing syndrome.

The third stage, which is the stage of gradual recovery, begins in the third month, irrespective of the type of treatment. The first indications of improvement are usually an increase in both appetite and sleep. The child becomes calm and tolerant instead of being miserable and antagonistic. He gradually regains his motor power and takes an interest in his surroundings. Several months elapse, however, before he is finally restored to normal health.

It is believed that there is no specific therapy, but great benefit is obtained by attention to the details of symptomatic treatment. Under favorable conditions the mortality is low, most patients recovering completely. BECK, Buffalo.

TEMPERATURE OF THE SPINAL FLUID IN PSYCHIC AND NEURO-ORGANIC DISEASES. C. DALSGAARD NIELSEN, J. belge de neurol. et de psychiat. **35**:83 (Feb.) 1935.

By means of a thermometer of the thermocouple type attached to a small stilet which was introduced into the spinal fluid through a lumbar puncture needle, Nielsen measured the temperature of the spinal fluid and compared it with the body temperature in thirty-two cases of psychologic conditions, twelve of arteriosclerosis and senile diseases, nine of syphilis, one of encephalitis and six of various diseases. Some of the patients had increased body temperature; others did not. The body temperature was recorded by a rectal thermometer. The average difference between the rectal and the spinal fluid temperatures for the whole series was +0.2 C.; the range of difference was from —0.5 to +1 C. (0.9 to 1.8 F.). The

temperature of the spinal fluid had a fairly definite relation to the rectal temperature and ran about 0.2 C. higher, but this appears to have no important clinical significance, and the authors admit that it is largely of theoretical interest.

WAGGONER, Ann Arbor, Mich.

CUSHING'S SYNDROME: HYPOPHYSEAL BASOPHILISM. C. ANDERSEN, J. belge de neurol. et de psychiat. **35**:148 (March) 1935.

Andersen reports the case of a woman, aged 45, who had rather marked hypertrichosis and a family history of hirsutism. During the three years before examination she had gradually lost her mental and physical faculties and complained of headaches and fatigue. A year before examination she had an attack of icterus with loss of consciousness. Following this attack there were considerable dysarthria and an increase in the mental difficulty. The menstrual flow had always been abundant, but during the period before examination the menses had been interrupted for several months at a time.

Physical examination showed a well developed, overnourished woman with a beard, a large amount of hair over the thighs and pubis and some on the arms and legs. She had a markedly protruding stomach, long thighs and a thick neck and was described as having the aspect of a "fat man badly built." There was a suggestion of gallop rhythm, with enlargement of the aortic arch. The blood pressure was 250 systolic and 130 diastolic. Examination of the blood gave essentially normal results. The blood sugar content was 112 mg. per hundred cubic centimeters. The cholesterol content of the blood was 20 mg. per hundred cubic centimeters. There was no roentgen evidence of osteoporosis. There was slight polyuria. Neurologic examination revealed exaggerated tendon reflexes with a positive Babinski sign, a positive Romberg sign and dysarthria. Examination of the spinal fluid gave negative results. A roentgenogram of the skull showed enlargement of the sella turcica with thinning of the posterior clinoid processes.

The author considers that this is a case of a pure Cushing syndrome without the addition of other endocrine factors, which he thinks have been present in most of the other recorded cases.

WAGGONER, Ann Arbor, Mich.

THE FUNCTIONAL INTERRELATIONSHIP BETWEEN THE ANTERIOR LOBE OF THE PITUITARY GLAND AND THE OVARIES. J. A. DUBOWIK, Arch. f. d. ges. Physiol. **235**:412, 1935.

Electrical stimulation of the anterior lobe of the pituitary gland furthers the maturation of the ovaries in axolotls, while extirpation of the pituitary gland induces hypoplasia of the ovaries. Injection of an extract of the anterior lobe in hypophysectomized animals induces maturation of the undeveloped ovum.

SPIEGEL, Philadelphia.

THE PERIPHERAL AUTONOMIC INNERVATION AND THE TROPHIC PROCESSES IN DOGS. N. F. POPOV, Sovet. psikhonevrol. **6**:31, 1934.

In this study an attempt is made to throw light on the trophic processes and their relation to the autonomic nervous system. Popov believes that the approach to the problem should begin with a consideration of the peripheral nervous system, as it is the phylogenetically older structure and, therefore, the essential one in the basic life processes. Popov carried out an experimental study on dogs in which he removed the influence of the central nervous system by cutting the spinal cord at the level of the fifth or sixth cervical segment, thus eliminating the influence of the higher portion of the central nervous system on the sympathetic chains. In addition, both vagus nerves were cut in the neighborhood of the thyroid cartilage. Such a preparation excludes entirely the influence of the central nervous system on the functions of the vegetative nervous system. After recovery of the animal, the metabolic processes, the regulation of the heart rate and the growth and the regeneration of tissue were studied. Except for the

absence of periodicity in the motility of the gastric wall, Popov found that all the autonomic processes were approximately normal. He therefore believes that the basic life processes are regulated by the peripheral nervous system.

In another series of experiments Popov studied the minute changes in the tissues and their relation to the central nervous system. For this purpose he cut the spinal cord at the level of the fifth cervical segment and a sympathetic chain on one side, thus cutting off all innervation of one hindlimb, leaving the connection of the other through the sympathetic innervation intact. The study of the physiologic and biochemical processes in both legs seems to indicate that the sympathetic component controls the catabolic processes and determines the increase in the muscle tonus and the threshold of excitability. In a third series of experiments the spinal cord was left intact, while a sympathetic chain was removed on one side. In such preparations Popov found an increase in tissue reserves, as evidenced by the determinations of the amount of glycogen, creatine and creatinine. He concludes that the parasympathetic division has an anabolic assimilatory function. He believes that Pavlov's hypothesis concerning the regulatory influence of the central nervous system on the tissue processes through the intermediary of the sympathetic and parasympathetic divisions is correct.

NOTKIN, Poughkeepsie, N. Y.

Treatment, Neurosurgery

MENINGOCOCCIC MENINGITIS: NEW FORM OF THERAPY. A. L. HOYNE, J. A. M. A. **104**:980 (March 23) 1935.

Hoyne has seen a reduction of 50 per cent in the mortality from meningococcic meningitis when meningococcus antitoxin was used intrathecally. A study is now under way to compare the efficacy of intravenous and intramuscular injection supplementing intrathecal administration of antitoxin. One young woman with a fulminating type of meningococcemia, whose child died of meningococcic meningitis, was treated only by large doses of antitoxin administered intravenously. Meningeal infection did not progress, and she was discharged completely recovered on the seventh day of hospitalization. For the treatment of meningococcic meningitis with meningococcus antitoxin, the author presents the following plan: 1. For intravenous administrations, from 60 to 100 cc. of the antitoxin is used in from 120 to 200 cc. or more, respectively, of physiologic solution of sodium chloride or a 10 per cent solution of dextrose. The smaller amount may suffice for a child and the larger quantity for an adult. This form of treatment may be repeated daily if the condition of the patient seems to require it. As a rule, one large dose intravenously when therapy is started will prove sufficient by this route. 2. For intraspinal administration the amount of antitoxin, undiluted and given by the gravity method, will be governed by the volume of spinal fluid withdrawn. Usually the quantity of antitoxin administered should be less than the amount of spinal fluid released. The initial dose of antitoxin administered intraspinally will usually vary from 20 to 40 cc. Daily punctures should be made until the fluid is clear and free from organisms. At such a time the cell count of the spinal fluid will generally be less than 100. 3. Intramuscular administration of serum in an initial dose of from 30 to 60 cc. is of value, but because of the serious nature of the disease the intravenous route is to be preferred.

EDITOR'S ABSTRACT.

TREATMENT OF SPASMODIC TORTICOLLIS WITH SPECIAL REFERENCE TO PSYCHOTHERAPY, WITH A REPORT OF A CASE. JOSEPH C. YASKIN, J. Nerv. & Ment. Dis. **81**:299 (March) 1935.

After a review of the literature on spasmodic torticollis Yaskin finds little that is definite concerning the pathology and the physiology. Foerster insisted that the condition is a manifestation of athetosis and is dependent on some acquired disease or congenital weakness of the striatum. The etiology is obscure. Removal

of infective foci has resulted in considerable improvement in many cases. Operations such as the section of the spinal accessory and posterior divisions of the first three cervical nerves usually give considerable relief, but unsuccessful results are often reported. No means of differentiating between spasmodic torticollis with and without an organic basis has yet been devised.

Yaskin reports the case of a man, aged 34, in whom there developed stiffness in the neck after a game of tennis; later, the head twisted to the left after the patient had been at a movie. The movements became so bad that two years after the onset he had to give up his business. Several neurologists recommended an operation. Physical and neurologic examinations gave negative results. There were no outstanding mental peculiarities. Nasal polyps were removed without altering the symptoms.

Sodium amytal was administered in fairly large doses with the object of weakening inhibitions to associations. The patient recalled that he had an abnormal attachment to his mother and that he slept with her between the ages of 9 and 14 years. He had an intense hatred of his father, whom he regarded as a bear. He recalled sitting on his father's lap at the age of 4 years when on a train. The father leaned out of the window and his head almost collided with a telegraph pole. He recalled vividly how the father jerked in his head. His criticisms of his father as a bear were always associated with tension and anxiety. Ever since he could remember he had tended to do things toward the left. Sexually, he had masturbated with other boys and had practiced sodomy, but after heterosexual relations at the age of 19 he found little gratification and considered himself impotent. After an automobile accident and business reverses he feared blindness, insanity and death. Blaming his condition on masturbation, he confessed to his father, who consoled him with the statement that he also had been impotent for twenty years. The patient often felt that his idea of blindness, death and insanity were unnatural, and he acquired the habit of dispelling them from his mind by shaking his head. As the torticollis subsided during treatment the patient became increasingly affected with a sense of tension and anxiety and with a fear of insanity, of going to bed and of being alone. The association touched on a homosexual relationship which the patient insisted had nothing to do with his torticollis, and he discontinued the treatment.

Yaskin stresses the faulty psychosexual development with varying anxiety as the cause of the torticollis in this case and advocates intense psychotherapy in cases in which definite organic causes cannot be demonstrated.

HART, Greenwich, Conn.

WHAT SHALL WE DO FOR THE PATIENT WITH TRIGEMINAL NEURALGIA? GILBERT HORRAX and JAMES L. POPPEN, New England J. Med. **212**:972, 1935.

The advisability of avulsion of the sensory nerve root as a primary procedure versus injections of alcohol is discussed. The views expressed are based on observations on 500 patients seen in the surgical service of the Peter Bent Brigham Hospital. Two hundred and four radical avulsions of the sensory nerve root have been performed without fatality or serious operative complication. Such postoperative difficulties as were observed occurred in patients who did not cooperate.

Seven hundred and sixty-nine injections of alcohol have been made on patients in this series. Deep injections at the foramen ovale for the relief of pain in the third division of the nerve composed the largest group. The average period of relief has been fourteen and three-tenths months; the longest, eight years; the shortest, nine months. When pain has been confined to the infra-orbital branches of the second division of the nerve, the injection has been made at the infra-orbital foramen, and the average period of relief has been twelve and two-tenths months. Miscellaneous sites of injections have been selected in the remainder of the cases.

In determining the indications for the different types of therapeutic procedures, due weight has been given to all the factors concerned in each patient. However,

no avulsion has been performed unless the patient has previously received injections of alcohol. The process of injection has been made an office procedure in order to minimize the cost to the patient. MOORE, Boston.

TREATMENT FOR PARKINSON'S SYNDROME WITH HIGH DOSES OF ATROPINE SULFATE (ROEMER METHOD). E. BAUER, J. GOLSE and G. MARQUET, Ann. méd.-psychol. **93**:420, 1935.

The treatment for the parkinsonian syndrome with atropine sulfate, a technic which has been in use in Germany for the last ten years, was tried by the authors. In the eight cases which they report rigidity diminished or disappeared completely, tremor diminished or disappeared in most cases, ocular spasms were reduced in frequency and intensity and salivation stopped. Of the mental symptoms, only the ones caused by the feeling of physical inferiority, such as depressive and hypochondriac states, were relieved, while irritability, impulsiveness and mental deficiency remained unchanged. In the authors' opinion the Roemer method is at present the best treatment available for the sequelae of epidemic encephalitis.

MOORE, Boston.

RESULTS OF THE COMBINED USE OF HEAT AND GOLD CHLORIDE IN TREATMENT IN THIRTY-FOUR CASES OF DEMENTIA PRAECOX. H. CLAUDE and J. DUBLINEAU, Ann. méd.-psychol. (pt. 1) **93**:553 (April) 1935.

Thirty-eight per cent of patients with dementia praecox were cured by alternate injections of a suspension of sulfur in oil (from 0.35 to 2.3 Gm.) and gold chloride (0.1 cc. of a 1 per cent solution). Albuminuria and erythema resulted in one case. The treatment included from ten to fifteen such injections, alternating with heat treatments. Cures were effected mostly in the manic type of patients who showed symptoms before 25 years of age. MOORE, Boston.

Special Senses

LECTURES ON MOTOR ANOMALIES OF THE EYES: II. PARALYSIS OF INDIVIDUAL EYE MUSCLES. A. BIELSCHOWSKY, Arch. Ophth. **13**:33 (Jan.) 1935.

This is the second of a series of lectures on motor anomalies of the eyes. From a neurologic standpoint, a discussion of the involvement of the individual ocular muscles is important only etiologically. The "nystagmus retractorius" of Körber—an even more interesting ocular phenomenon than the "pseudo-Graefe" syndrome which is seen occasionally in patients when they are recovering from oculomotor paralysis—is discussed briefly. In a consideration of the pseudo-Graefe phenomenon Fuch's explanation is given as follows: Because the nucleus of the third nerve is injured or in consequence of a retrograde degeneration has become atrophic, the nervous stimulation sent to a part of the third nucleus overlaps the neighboring parts, so that the latter are stimulated and unintended movements are obtained. Bielschowsky believes that this pseudo-Graefe sign can be explained in a less far-fetched manner. In the course of healing from some form of trauma, some of the nerve fibers which proceed from the central part of the trunk of the third nerve do not find their original sheaths in the peripheral part of the nerve but go astray, so that they arrive at muscles to which they do not belong. For instance, the fibers from the nucleus intended for the internal rectus muscle arrive not at that muscle but in the levator muscle of the upper lid, so that the impulse for adduction produces elevation of the lid even when it cannot be elevated by a direct innervation effort because of fibers coming from the levator nucleus have either gone astray or died. In this way all types of unintended movements may appear. It seems, however, that the nerve fibers in the course of healing prefer certain routes for growing into the wrong sheaths, so that in the majority of cases the impulse to look downward and inward produces the strongest contraction of the levator muscle of the upper lid. SPAETH, Philadelphia.

OCULAR DIVERGENCE: ITS PHYSIOLOGY AND PATHOLOGY. G. M. BRUCE, Arch. Ophth. **13**:639 (April) 1935.

This is an ophthalmologic review covering the history and experimental work in the physiology and pathology of ocular divergence. The bibliography is extensive. The literature is well reviewed. Insufficiency and excess of divergence are both well covered.

Considered only on the basis of a review of the literature, the author's theory is that there certainly are physiologic, phylogenetic and pathologic grounds for claiming the existence of a center for ocular divergence. It may be asked why, if a center for divergence really exists, active voluntary divergence is not possible. It seems that the universal response to this question is apt. There is apparently not enough biologic advantage in such a function to justify its acquisition and its development. From certain physiologic findings this center, if it exists, lies separate from, but adjacent to, the nucleus of the abducens nerve. Since the external rectus muscles are innervated only ipsilaterally, this nucleus would probably be in the midline.

SPAETH, Philadelphia.

TRAUMATIC ANGIOPATHY OF THE RETINA (PURTSCHER'S DISEASE). M. AMSLER, Ann. d'ocul. **171**:568 (July) 1934.

Traumatic angiopathy of the retina, which was first described by Purtscher in 1910, is rare. The ophthalmoscopic picture is characterized by white spots in the region of the posterior pole of the eye. They may be compared with flakes of snow or cotton and with accumulations and bundles of myelin fibers. The white milky or silvery spots, which vary in form and size (from 0.3 to 0.7 mm.) are isolated or confluent and are usually situated along veins, which they cover partially or almost completely, thus proving their superficial position in the retina (Vogt).

Purtscher's disease is an indirect traumatic disease due to a lesion at a distance. The exciting injury does not directly affect the eyeball. The usual injury is cranial trauma (occurring in twenty-four of thirty cases) with or without fracture or loss of consciousness, caused by a fall or shock affecting the vertex, the occiput, the temporal region or the face. Compression of the thorax plays an important rôle in the etiology in some cases of traumatic angiopathy of the retina. Schneider's case is typical of this group. In this instance thoracic compression received when the patient was crushed between two railroad cars resulted in Purtscher's disease bilaterally. Rados' case, in which a horse fell on his rider, also supports this theory.

Of thirty patients with traumatic angiopathy of the retina whose cases were reported in the literature, twenty-nine were men between the ages of 16 and 57, the majority being between 20 and 30. In one case the patient was a girl, aged 4 years, who had been crushed by an automobile.

At the time of the trauma and immediately after it, visual disturbances appear, e.g., clouding of vision in one or in both eyes. This blurring of vision may remain stationary or may gradually diminish after a few days. At the time of the first examination, from nine hours to fifteen days after the accident, central visual acuity was below 0.1 in fifteen cases, between 0.1 and 0.4 in twelve cases and between 0.5 and 0.6 in seven cases, and in two cases it was 1.0. A central scotoma or one or more paracentral scotomas were usually noted.

In summarizing the pathogenesis of traumatic angiopathy of the retina, Amsler reports two theories: 1. The cranial theory (of Purtscher and Vogt), which the majority of ophthalmologists accept, relates the disease to hypertension of the cerebrospinal fluid and choked disk. Purtscher believed that the white spots were retinal lymphorrhagias caused by intense and sudden hypertension of the cerebrospinal fluid. This hypertension diffuses, entering the ventricles and subarachnoid space and passing between the sheaths of the optic nerve as far as the lymphatic sheaths of the central vessels of the retina and its intra-ocular branches. These sheaths rupture, resulting in lymphorrhagia. 2. The ocular theory (Stähli, Best and Marchesani) ascribes Purtscher's disease to a contusion of the eyeball

which leads to the association of the white spots which occur in Purtscher's disease with Berlin's disease. Amsler believes that Purtscher's traumatic angiopathy of the retina is different from Berlin's disease.

BERENS, New York.

STUDY OF THE VISUAL FIELD IN SYNDROMES ASSOCIATED WITH THE THYROID GLAND. DROUET, JEANDELIZE and GAULT, Ann. d'ocul. **172**:233 (March) 1935.

Drouet, Jeandelize and Gault state that of eleven patients with hyperthyroidism four showed temporal contraction of the visual field bilaterally before treatment. Of three patients on whom thyroidectomy had been performed, two presented temporal contraction bilaterally. Of four patients with parathyroidism, there were three with temporal contraction bilaterally for white and one for red and green. Two patients with essential arterial hypertension showed temporal contraction bilaterally. One patient with migraine showed a slight contraction during the attack and an enlargement afterward.

BERENS, New York.

SEMEIOLOGIC VALUE OF RETINAL ARTERIAL PRESSURE IN THE COURSE OF INTRACRANIAL HYPERTENSION. P. GUILLOT and J. PAILLAS, Rev. d'oto-neuro-opht. **13**:265 (April) 1935.

Claude, Lamarche and Dubar have shown that the retinal diastolic pressure is normal when papillary stasis begins. Guillot and Paillas studied eighty-seven cases in which syndromes of intracranial hypertension were present. Examination of the papilla or of the retinal circulation revealed the accompanying hypertension of the cerebrospinal fluid. In seventy of the cases the papillary stasis was such that measurement of the retinal arterial pressure was impossible or useless. In six of the remaining seventeen cases the observation of solitary retinal arterial hypertension preceded the establishment of the stasis; in one case it accompanied the appearance of the disk described as "contour physiologically hazy," and in still another case retinal arterial hypertension lagged behind the increasing arterial tension. Two cases of established stasis were observed in which the retinal arterial tension was proportionate to the stasis. In four cases in which stasis in evolution was observed there was a normal retinal arterial tension. The fourth group contained three cases in which, after operation (lumbar puncture, craniectomy and ventricular puncture), lowering of the retinal arterial tension preceded the regression of stasis. Measurements of retinal arterial tension may permit a diagnosis of intracranial hypertension when stasis is not perceptible or is doubtful; they are also useful in controlling the efficacy of depletive treatment. The authors warn that a negative result of the measurements is not to be interpreted one way or the other. Their greatest usefulness will be in cases of cerebral tumor in which early diagnosis and localization are important.

DENNIS, San Diego, Calif.

OCULAR MANIFESTATIONS OF SUPPURATIVE OTITIS. H. TILLÉ, Rev. d'oto-neuro-opht. **13**:325 (May) 1935.

This study is divided into two chapters: (1) diseases of the trigeminus nerve and the oculomotor nerves and (2) edema of the papilla and retinal arterial hypertension. Paralysis of the orbicularis and of the facial nerve in general and vestibular nystagmus are not considered. The importance of a thorough examination, especially when there is partial paralysis of the third nerve, of careful and repeated observations of the eyegrounds and of retinal tensions is emphasized. The author's conclusions are: The most frequent type of oculomotor paralysis is that of the abducens nerve. After acute otitis media, from which lesions are propagated to the abducens nerve at the petrous tip, the syndrome of Gradenigo, with its classic triad, otitis media, pain in the temporofacial region and paralysis of the abducens nerve, appears. At times the clinical aspect is slightly different;

there is either heterolateral paralysis of the sixth nerve or associated involvement of the other oculomotor nerves, or there is chronic suppuration of the mastoid, which extends into the petrous process or along the pharyngeal wall by way of the lacerated foramen. Sometimes there is osteitis of the tympanum or perilabyrinthine osteitis with anterosuperior petrositis, manifesting itself clinically by involvement of the trigeminus nerve. Papilledema is a symptom of capital value when present. It signifies intracranial hypertension but is infrequently encountered. On the other hand, there is no generalized or localized intracranial hypertension without retinal arterial hypertension. General and local intracranial hypertension would be recognized earlier by otologists during the course of treatment for complications of suppurative otitis if more consideration were given to the study of retinal arterial tension. In every case of otitis a curve of retinal arterial tensions should be established. It is definitely the curve of intracranial pressure. A well established retinal hypertension signifies intracranial hypertension, even if all other signs are negative, including the results of lumbar puncture. Papilledema is inconstant, but retinal hypertension is never lacking. It is observed from the onset in all complications of otitis media in which intracranial hypertension is present. Papilledema is manifested after a period of latency of several days or weeks; its regression after cure requires several months. It is seen especially in (1) thrombosis of the cavernous sinus following thrombosis of the lateral sinus in cases of acute scarlatinal otitis and in (2) abscess of the brain and especially of the cerebellum, which is almost always of auricular origin. The ocular signs are retinal hypertension, papilledema and paralysis of the abducens nerve. The diagnosis is based clinically on the following facts: chronic suppuration of the ear, a normal or elevated temperature, a slow pulse rate of from 40 to 45, torpor, emaciation and cerebellar signs.

Other ocular symptoms are much less frequent in the complications of otitis. Homonymous hemianopia or quadrantanopia may be observed in association with lesions of the middle cerebral fossa. These signs must be delimited daily in the interests of operative opportunity. In the syndrome of Parinaud (paralysis of upward gaze with or without paralysis of convergence) the lesion is in the neighborhood of the quadrigeminal bodies. Other ocular symptoms are paralysis of lateral gaze and conjugate deviation of the head and eyes, the localizing value of which is at present practically nil, the topography of the oculomotor pathways behind the nuclei not being well known.

The otologist, particularly when there is a suspicion of a complication of suppurative otitis, should demand a complete ophthalmologic examination and a precise response to the following questions: 1. Is there stasis, even of the discrete type? Is there retinal arterial hypertension as determined by several measurements, extending if possible over several days? The existence of one of these symptoms indicates a generalized or localized intracranial hypertension, whatever may be the result of the direct measurements of the tension of the cerebrospinal fluid. 2. Is the trigeminus nerve involved, and what is the probable location of the lesion? Anesthesia of the cornea should be systematically sought; the various sectors of the cornea should be explored. The ocular pains must be analyzed to determine if the case is one of classic facial neuralgia or of the syndrome of Sluder, or of migraine due to vasomotor meningeal disturbances. 3. What is the state of the internal and external musculature of the eyes? 4. What is the state of the central and peripheral visual fields? 5. Does the lateral sinus seem to be permeable? Does compression of the jugular veins cause a preexisting retinal venous pulse to disappear, or does it make it appear? Does it augment the pressure in the central vein of the retina? The investigation of all these symptoms demands great patience and special clinical training. The examination permits the oculist to say whether there is intracranial hypertension, whether there is involvement of the trigeminal, abducens or oculomotor nerves, whether there is a lateral homonymous hemianopia from a high or low temporal lesion and whether the sinojugular channels are open.

DENNIS, San Diego, Calif.

RETINITIS PROLIFERANS AND INCREASED INTRACRANIAL PRESSURE. P. KIEWE, Schweiz. Arch. f. Neurol. u. Psychiat. **35**:41, 1935.

The two cases of retinitis proliferans here reported are considered to be of particular interest because both patients were older than usual and neither had syphilis, tuberculosis or diabetes mellitus. Both were suffering from severe hypertension. The initial spinal fluid pressures, measured with the patient in the reclining position, were 660 and 360 mm. of water, respectively, this being the only direct evidence of increased intracranial pressure. Kiewe expresses the view that hypertensive changes in the walls of the retinal arteries may have interfered with the absorption of hemorrhagic exudates, which, in turn, stimulated the proliferative process.

DANIELS, Denver.

THE STRUCTURE OF THE OCULOMOTOR NERVE. E. D. BROMBERG, Sovet. psikhonevrol. **6**:38, 1934.

Bromberg made a microscopic study of the main trunk of the third cranial nerve, as well as of the superior and inferior branches, the ciliary nerves, the anastomosis with the ophthalmic nerve and the fibers supplying the sphincter pupillae and the dilator pupillae. The main trunk of the oculomotor nerve consists predominantly of thick, medium and fine medullated fibers. In addition, there is a small number of parasympathetic fibers running singly in the form of spirals around the medullated fibers, and finally, there are also a very small number of sympathetic fibers running in fascicles. The anastomosis with the ophthalmic nerve shows the same composition. The ciliary nerves consist chiefly of sympathetic fibers. There are only a few fine and a few medium-sized medullated fibers, with an equal number of parasympathetic fibers. The fibers going to the sphincter pupillae are predominantly parasympathetic, with only two or three medullated fibers. There are about five to twenty fibers altogether. The fibers supplying the dilator pupillae are for the most part sympathetic in type, with from two to five small and medium-sized medullated fibers.

NOTKIN, Poughkeepsie, N. Y.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

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FRANCIS C. GRANT, M.D., *Chairman*

VALUE OF ENCEPHALOGRAPHY IN THE DIAGNOSIS OF ATROPHY OF THE FRONTAL LOBE. DR. BERNARD J. ALPERS.

This case is presented in order to point a moral. The facts can be stated briefly, because they have little to do with the point to be made. A man aged 48 was admitted to the Philadelphia General Hospital to the ward for persons with disorders of metabolism, on Sept. 23, 1933, and was transferred to the ward for patients with nervous diseases on September 28. He had had a stroke about a year before. He made a good recovery and regained the power of his limbs. He had also had trouble with speech for a year. On admission he had diabetes, with a blood sugar level of 380 mg. per hundred cubic centimeters, peripheral arteriosclerosis and enlargement of the heart and liver. Neurologic examination on several occasions revealed signs of cerebellar involvement. These signs were noted in the limbs and the trunk and were so marked as to attract immediate attention. More specifically, there were severe asynergia of all the limbs and the trunk, past pointing and rebound phenomena, dysmetria, an ataxic gait and a Romberg sign. Speech was severely dysarthric and explosive. All the tendon reflexes were markedly hyperactive, and there was a Babinski sign bilaterally. There were atrophy of both optic nerves, weakness of the central part of the left side of the face and weakness of the palate. There was no loss of power in the limbs and no disturbance of deep sensation. The inability to walk was due entirely to the cerebellar dyssynergia.

The signs of cerebellar involvement were so pronounced that it was decided that there was primary disease of the cerebellum, possibly softening or even a hereditary type of disturbance. The atrophy of the optic nerve and the hyperactive reflexes made a diagnosis of multiple sclerosis possible. It was decided to make an encephalogram for the following reasons: 1. There was no tumor of the posterior fossa. 2. While softening in the cerebellum was a diagnostic possibility, the marked signs of cerebellar involvement which were present are never seen in this condition. 3. If cerebellar atrophy was present, it would be easily visible after the injection of air.

An encephalogram, made in September 1933, revealed intense atrophy of the frontal lobes. There appeared to be no involvement of the cerebellum.

The patient became progressively worse and died on Oct. 3, 1935. Necropsy revealed softening in the left cerebellar hemisphere. Of greatest importance, however, was the mild or, at most, only moderate atrophy of the frontal gyri. There was much less atrophy than the encephalogram indicated; in fact, the frontal gyri were well within the range of normal for the patient's age. At necropsy a layer of fluid, about 2 cm. thick, was found in the subarachnoid space in the frontal lobes. This had apparently separated and compressed the gyri to such a degree as to give the appearance in the encephalogram of intense cortical atrophy. The criticism may be raised that the atrophy present in life was obscured by the terminal edema of the brain. Granting that edema of the brain was present, it was not enough to fill out frontal lobes that were as completely atrophied as the encephalograms show them to be.

This case illustrates, if illustration of this point is necessary, that the encephalogram is not too accurate an index of cortical atrophy. In the first place, lacking

normal standards for various age levels, one cannot state accurately whether a given degree of cortical atrophy is or is not significant. Second, the case reported teaches that atrophy of the brain as shown by encephalography cannot be accepted without further argument. The encephalogram may be said to be of value only if it conforms with the rest of the clinical evidence.

DISCUSSION

Dr. H. E. Riggs: I wish to corroborate what Dr. Alpers said. I examined the brain before it was removed from the head and found external hydrocephalus measuring roughly 2 cm. in thickness. There was only mild cortical atrophy. There was edema, but not sufficient to mask an underlying atrophy. There was a scar of an old vascular lesion involving the tentorial surface of the right cerebellar hemisphere and extending into the dentate nucleus. There was also an old vascular lesion involving the right internal capsule and the adjacent caudate nucleus and the putamen. The most striking feature was the intense atheroma of the large cerebral vessels, with concentric reduction of the lumen.

Dr. Temple Fay: I think that all have seen the variation that occurs between encephalographic markings obtained on the same patient when subsequent examinations have been made. Frequently the wide markings suggestive of atrophy that are seen on the initial film appear to approach the normal pattern, and in my opinion this is due to an increase in the volume of blood in the cerebral circulation. The brain becomes more "plump," and I am inclined to interpret this change as one would the tissue change that occurs in the hand following the removal of a tight glove. As circulation returns, the part tends to approach its normal limits of volume.

In the light Dr. Rigg's report, I think that the final diagnosis of external hydrocephalus must be questioned, as the terminal swelling might have been edema.

Can Pain of Thalamic Origin Be Relieved by Chordotomy? Dr. Charles H. Frazier and Dr. F. H. Lewy.

This short communication does not permit a definite answer to the question asked in the title. However, the case to be presented offers a rare opportunity for one to explore the problem of the physiology of pain in man.

Three theories are prevalent concerning pain of thalamic origin. The oldest theory is based on the assumption that a lesion acts as a constant stimulus on the pain-conveying elements in the optic thalamus. The second theory, that of Head and Holmes, on the other hand, is based on the idea of liberation of the thalamic pain apparatus by interruption of an inhibitory corticothalamic tract. The third theory is based on clinical experience obtained in cases of lesion of the tracts of Goll and Burdach. Foerster advanced the idea that the destruction of what he calls the perceptive-epicritic system of sensibility, the neosensibility of Brouwer, comprising the kinesthetic, pressure and discriminating sense, was responsible for hyperpathia and pain of thalamic origin.

Mrs. K., aged 63, an intelligent woman, suffered for several years from high blood pressure (210 systolic and 100 diastolic), diabetes, headache, scintillating scotoma and pains in the eyes. In 1933 she had a stroke. At that time she had complete left hemiplegia with dysarthria and excruciating pain in the entire left side of the body from the vertex over the face, neck and extremities down to the toes. While there was almost complete recovery from the hemiplegia and dysarthria, the pain persisted and defied all therapy. At the time of admission to the Hospital of the University of Pennsylvania the patient took as much as 9 grains (0.6 Gm.) of morphine daily without complete relief from pain.

Two forms of pain were differentiated by the patient as follows: 1. There was a constant intense pain "as if red hot lava were running over my shoulder, hands and toes" or "as if hot lead were poured into the palm of my hand." At the

left side of the face she felt a sensation "as if icy water was trickling over my cheek" or "as if an ice plate was pressed against my face." 2. Two or three times a day an attack occurred during which she experienced electric shocks passing through the left side of the body.

Despite the spontaneous pain and dysesthesia, there were extensive though not complete anesthesia and analgesia of the entire left side, with loss of position sense and with astereognosis. Some scattered touch and pain points were elicitable, and there were an increased threshold for pain, an explosive reaction, a long after-effect and wide radiation of pain typical of the manifestations of thalamic lesions.

The patient insisted on surgical intervention and threatened to commit suicide in case of refusal. We were guided in our decision by experience with major trigeminal neuralgia, which we believed might be the result of a thalamic lesion. If this assumption was true, blocking the fifth nerve should relieve the pain in the face. On May 27, 1935, Dr. Frazier injected alcohol into the left gasserian ganglion with immediate and complete relief from all pain and all paresthesia in the three divisions of the fifth nerve, while the adjacent area of the second and third cervical nerves became more painful than ever. Although the face was almost anesthetic and analgesic before the injection of alcohol, the patient complained of numbness after the injection.

Since interruption of the fifth cranial nerve had proved so helpful in relieving pain, the next step was to try the effect of spinal anesthesia. To our surprise this procedure was ineffective, and the pain increased. This may be explained in accordance with the experience that a lesion of the tracts of Goll and Burdach increases or produces pain, as was demonstrated by Brown-Séquard. With this negative result in mind, chordotomy was suggested. On July 3 Dr. Frazier divided the right anterolateral column in the fifth cervical segment. At the same time the second and third left cervical posterior roots were crushed. The chordotomy itself was unusually painful.

For about two weeks after the operation the patient had gradually decreasing pains in the right arm, but the left side of the body and left extremities were completely free from pain and dysesthesia. Two days after the operation it was possible to cut down the daily dose of morphine from 9 to 2 grains (0.6 to 0.12 Gm.). The patient left the hospital on July 16, free from pain in the left side and able to walk. The relief continued for a couple of weeks, when the pain reappeared in the left shoulder, arm and leg, but not in the face. However, the patient's physician wrote on September 20 that despite her pain she did not need to use morphine. We presume that the degree of pain is less than before operation.

It is well known that in cases of thalamic lesions in which there are attacks of pain the paroxysm is elicited eventually by stimulation of the healthy side. Therefore, we were not surprised that unilateral chordotomy was not permanently effective. We believe, however, that bilateral chordotomy supplemented by blocking the fifth nerve may give a lasting effect.

In the meantime the physiologic result seems of signal interest. In this case pain of thalamic origin was relieved by interruption of the afferent pain fibers in the anterolateral tracts for a period certainly outlasting the duration of the operative shock. This experience implies that in the presence of a thalamic lesion peripheral stimuli—possibly subliminal under normal conditions—become supraliminal and even painful. In other words, peripheral stimuli seem to be indispensable for the production of central pain. The theory that a continuous stimulation of the thalamic pain apparatus is essential should therefore be abandoned. The fact that spinal anesthesia, involving all qualities of paleosensibility and neosensibility, increased the degree of pain speaks in favor of Foerster's conception and against the theory of Head and Holmes.

To sum up, we conclude from this experience that pain of thalamic origin is the result of two factors: (1) continuous slight stimulation of the peripheral proprioceptive, pain and temperature fibers and (2) a lesion of the pain-damping system of the posterior spinal tracts within the optic thalamus. Sufficiently extensive surgical interruption of the pain fibers in the anterolateral columns, leaving

intact the posterior roots, horns and tracts, may be a method of obtaining relief from these unbearable and up to now incurable pains.

DISCUSSION

DR. C. H. FRAZIER: Dr. Lewy has emphasized the important significant facts connected with the problem of pain of thalamic origin and the possibility of its relief. One should not be asked to draw final conclusions from the single clinical observation. At the same time, relief from pain of this intolerable character was so striking and dramatic that we believe we may have found a solution, and since there is more than one tract for conducting fibers of pain sensation it may be possible in all these cases to perform bilateral rather than unilateral chordotomy.

DR. H. C. BAZETT: May I ask whether there were any changes in temperature sense after chordotomy?

DR. F. H. LEWY: I am sorry that I cannot answer Dr. Bazett's question.

A NEW METHOD FOR REDUCING INTRACRANIAL PRESSURE. DR. JOSEPH HUGHES, DR. STUART MUDD and DR. EDWARD A. STRECKER.

Lyophilic human blood serum, redissolved in a concentrated form so as to make a hypertonic solution, has been used to reduce intracranial pressure. Lyophilic serum is serum that is dried in vacuo from the frozen state (Flosdorf, E. W., and Mudd, Stuart: *J. Immunol.* **29**:389, 1935). Resolution occurs readily on the addition of distilled water. In order to make the serum safe for intravenous administration, as in the present experiment, an extra step is introduced in the process; namely, the redissolved serum is passed through a Berkefeld N or W filter in order to remove the aggregates of chylomicrons which form as a result of the processing of lyophilic human serum.

When given intravenously in doses of from 25 to 50 cc., serum thus concentrated caused a temporary rise in the cerebrospinal pressure during the period of injection, as measured by lumbar puncture, followed by a prolonged fall in pressure. As compared with 50 cc. of a 50 per cent solution of dextrose, 25 cc. of human serum, twice concentrated, reduced intracranial pressure to a greater degree and over a longer period of time. The increased effectiveness of concentrated serum over a 50 per cent solution of dextrose may be due to its content of proteins which cannot diffuse out of the vessels as readily as dextrose. No untoward results have developed from the intravenous injection of concentrated serum.

At the present time, in order to increase the osmotic properties of this type of concentrated serum preparation, a 50 per cent solution of dextrose is being used instead of distilled water to redissolve the dried serum; likewise, in the present product the serum is concentrated four times instead of twice.

The question of blood typing is not important when concentrated serum is given slowly in doses of 50 cc. because of the relatively small amount of such an injection in comparison with the total volume of blood.

DISCUSSION

DR. H. C. BAZETT: It seems to me of interest that an injection of a small volume of serum of only twice normal concentration should have a perceptible effect; one would not expect it to absorb more water than sufficient to make it up to its original volume. One can only suppose that a large proportion of the fluid absorbed comes from the cerebrospinal system.

DR. TEMPLE FAY: In my opinion, Dr. Hughes' contribution to the subject of dehydration is important, not only because it is physiologically sound but because it shows the ability to obtain a concentration of fluid into blood volume by utilization of natural protein affinities.

Dr. Hughes did not indicate the proportion of fluid which may be subtracted from other body tissues. In all probability a strict control of fluid intake will be

required in addition, in order to enhance the subtraction of fluid from the cerebrospinal fluid system.

I wish to ask if sufficient animal experimentation has been carried out to determine whether the fluid absorbed and the consequent fall in cerebrospinal fluid pressure is due to loss of fluid from the subarachnoid space or from the cellular brain mass per se. If edema and excess fluid can be removed from cellular tissue by this method, it will be an important measure in the accomplishment of dehydration, as the agents now available fail to reach the fluid locked within a cellular membrane.

DR. MATTHEW MOORE: There are certain conditions, in particular cerebral trauma, wherein it is necessary to reduce increased intracranial pressure at repeated intervals over an extended period of time. How frequently can this material be given with impunity in such conditions?

DR. C. H. FRAZIER: Has this method been used in cases of intracranial pressure in human beings?

DR. F. C. GRANT: I wish to raise two questions, first, whether or not this method has been used in human beings, and second, whether the estimations of intracranial pressure were obtained by lumbar puncture under controlled conditions.

DR. JOSEPH HUGHES: We used concentrated human serum. The intracranial pressure is estimated by lumbar puncture continuously and is recorded visually on a cerebrospinal fluid manometer, with the patient lying flat in bed during a period of forty minutes.

How frequently one can give concentrated human serum I can answer only by surmise. It is not antigenic, nor does one have to fear a reaction to foreign protein. If one were to give large amounts of concentrated serum, the possibility that different blood groups might be present should be considered. In such instances serum of the same type as that of the patient should be used. It is needless to point out that experimental data are not available to answer exactly how much concentrated serum can be used. It must be established by further experimentation. When used on human beings at the present time, it must be used with caution.

RELATION OF THE CEREBRUM TO THE CEREBELLUM: II. CEREBELLAR TREMOR IN THE MONKEY AND ITS ABSENCE AFTER REMOVAL OF THE PRINCIPAL AREAS OF THE CEREBRAL CORTEX (AREAS 4 AND 6A, UPPER PART); III. ACCENTUATION OF CEREBELLAR TREMOR FOLLOWING LESIONS OF THE PREMOTOR AREA (AREA 6A, UPPER PART). DR. CHARLES D. ARING and DR. JOHN F. FULTON, New Haven, Conn.

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DISCUSSION

DR. G. P. MCCOUCH: This paper raises so many points of interest that it is hard to know which to choose to discuss. I shall discuss two points which have not been emphasized very strongly but which seem to me of considerable interest. I wish to pay tribute to any one who can perform both of these operations on the same animal with survival of the animal. In my opinion it is a remarkable achievement, and it seems to me that the next step is to prolong the achievement still further. I question whether any animal which has had these two operations, regardless of the operator, has survived to the stage of equilibrium. I question whether the capabilities of such a preparation for surviving indefinitely are yet known. The other point refers to the interpretation of what Luciani called the dynamic stage, the first stage after decerebellation, in which the animal on which the operation has been properly performed goes into a state closely resembling decerebrate rigidity, that is, a state in which, as in the decerebrate animal, there are exaggeration of the labyrinthine tonic reflexes, loss of tendon reflexes and

loss of the supporting reaction. As the animal recovers, reactions characteristic of those seen in the decerebrate animal disappear, and one wonders whether that first stage should not be interpreted as essentially a state of diaschisis, which is similar to spinal shock, and whether or not these various reflexes are temporarily in abeyance as a result of the loss of the tracts which are concerned. One is tempted to speculate because when the reactions do return they return in an exaggerated form, much as spinal reactions do.

Rademaker's technic was the reverse; the cerebral operation was performed first, followed by the cerebellar operation. The first stage after cerebellectomy in Rademaker's dogs was more prolonged than in dogs which underwent cerebrectomy alone. In Dr. Fulton's animals there is, after the second operation, which consists of removal of the cerebrum, a recrudescence of much this same picture, and so it would look as if there are several sources of innervation which are important for the righting reflex and supporting reaction. The removal of one source would cause diaschisis, but removal of the second source after recovery from the effects of the first would produce the shock effect.

DR. ALFRED GORDON: From the clinical side there are two groups of cases: cases of tumor of the frontal lobe with atrophy of the opposite side of the cerebellum, which explains the ataxic symptoms, and cases of "cerebellar manifestations" associated with lesion of the frontal lobe, without lesion of the cerebellum itself. Prior to Dr. Fulton's era, Bárány and Delmas-Marsalet found experimentally that irradiation of the frontal lobe or exposure of the frontal lobe to extreme cold produced ataxic phenomena and loss of equilibrium. In 1917 and 1934 I put on record 5 anatomicoclinical cases in which the patients presented distinct manifestations of cerebellar involvement (*J. Nerv. & Ment. Dis.* **46**:261, 1917; **79**:411, 1934). The cases were extremely puzzling from the standpoint of localization. Anatomic studies showed that the frontal lobes alone were involved. I think that the majority of cases on record (experimental as well as the clinical investigations of authors such as Kitzig, Oppenheim, Duret, Horsley, Barraquer and Barré) indicate that the frontal lobe could be considered per se as a center of equilibration and orientation. I am particularly interested in the subject and want to ask Dr. Fulton and Dr. Aring what opinion they have formed from their experimental investigations—whether they do or do not consider the frontal lobe as a center of equilibration.

DR. J. F. FULTON: I am grateful for the remarks of Dr. McCouch, Dr. Bazett and others concerning the work just reported and also for Dr. Gordon's questions and comment with regard to the duration of the survival of decerebellate-thalamic animals following the final surgical procedure. In the cats the longest survival was sixteen days. The animals died not from infection of the wound or from physical exhaustion but from decubitus sores caused by the extraordinary activity which these preparations exhibited. The thalamic-decerebellate cat is a most formidable animal to care for; it has a tendency to get into preposterous positions and to make friction sores on the hips and ankles. We have had some success in these experiments in keeping such animals in hammocks, and it was obvious that the essential problem was one of nursing care. I am sure one can keep such animals alive for an indefinite period if they are adequately tended. The animal which survived till the sixteenth day was in perfect condition up to the fourteenth day, and then cellulitis developed. I entirely agree with Dr. McCouch that these preparations had probably not reached a state of equilibrium, but the "dynamic" manifestations of Luciani were gone by the fifth day after decerebellation. As to the influence of the various levels of activity of the central nervous system on the positive supporting reaction, there is room for much more detailed study; one can affirm only that the phenomenon occurs in the thalamic-decerebellate animal.

Dr. Gordon has asked an extraordinarily difficult question. I might say that after the production of these lesions atrophy of the cerebellar hemisphere, not marked, was occasionally seen; in animals which had survived for three years

after the loss of one cerebral hemisphere there was invariably some diminution in size of the opposite cerebellar hemisphere. Whether one of the manifold functions of the frontal lobes is that of equilibration I do not know. Delmas-Marsalet presented a paper at the International Neurological Congress in which this matter was discussed at some length, and his evidence was impressive. In monkeys there are marked disturbances of motor function, but whether in the last analysis this is really to be interpreted as a disturbance of equilibrium I am not prepared to say.

NEUROLOGICAL SOCIETY OF PARIS

Nov. 7, 1935

PROF. A. BARBÉ, *in the Chair*

REVUE NEUROLOGIQUE **64**:679 (Nov.) 1935

ABSTRACTED BY WALTER FREEMAN, M.D., WASHINGTON, D. C.

STATUS EPILEPTICUS WITH OBSTRUCTION OF THE BASILAR ARTERY AND ITS BRANCHES IN A CASE OF INTERNAL HYDROCEPHALUS. A. BARBÉ and A. BRIZARD.

A girl aged 6 years, who probably had congenital syphilis, had an attack of meningitis at the age of 6 months; this was followed by hydrocephalus and arrested development, both physical and intellectual, accompanied by convulsive seizures. Status epilepticus developed, and the patient died in six hours. The brain weighed 1,500 Gm. and showed marked dilatation of the ventricles; in addition, there were obliterative endarteritis of the basilar artery and its branches and evidence of terminal thrombosis.

ACUTE POLIOENCEPHALITIS IN A CHILD. G. GUILLAIN, P. MOLLARET and L. BERTRAND.

A child aged 8 years became ill, with disturbance in attention and later with sensory aphasia, disturbances in swallowing, a hypomanic state followed by catatonia and generalized rigidity without signs of pyramidal or extrapyramidal involvement. Terminally there were complete dysphagia, marked sweating and sialorrhea, rhythmic clonic movements of the limbs, jacksonian crises and hyperthermia. Histologically, there were perivascular accumulations of lymphocytes and plasma cells, extending from the cortex to the midbrain, and intense degenerative cellular changes. On the other hand, there was no disturbance in the myelin and only slight reaction in the neuroglia. The olives were markedly involved.

The infectious nature of the disorder was proved by the fact that all tests gave negative results except that there was an increasingly positive colloidal benzoin curve.

MYCOTIC ABSCESS OF THE FRONTAL LOBE. G. GUILLAIN, I. BERTRAND and J. LEREBOULLET.

A woman aged 33 after delivery suffered from sciatica on the left side and three weeks later from severe headache. A month later there appeared exophthalmos on the right and diplopia, followed in two weeks by reduction in vision. Serologic tests were negative, and antisyphilitic treatment was ineffective. Roentgenograms of the skull showed no osseous abnormalities. There were anesthesia of the right cornea and of the upper part of the face and mild paralysis of the left side, affecting particularly the lower part of the face. The spinal fluid con-

tained 8 lymphocytes per cubic millimeter. A diagnosis was made of a lesion in the region of the sphenoid fissure, probably a tumor, and the patient was treated with roentgen radiation. The patient died showing symptoms of acute asphyxia.

At necropsy there were seen marked adhesions below the right frontal lobe, and the whole region of the sphenoid fissure and cavernous sinus showed a plastic exudate. An abscess the size of an olive was found in the base of the right frontal lobe. In the pus there were various filaments, but no sulfur granules and no definite organisms could be made out. Similar conditions are rarely encountered.

HYDROCEPHALUS PRODUCED BY A LESION OF THE CHOROID PLEXUS OF UNDETERMINED ORIGIN RESEMBLING TUBERCULOSIS. G. GUILLAIN, I. BERTRAND and J. LEREBOULLET.

A woman aged 34 became ill with amenorrhea, headaches and vertigo; later there appeared projectile vomiting and difficulty in walking, the patient showing a tendency to fall toward the right. Examination showed choked disks. The spinal fluid was under 220 mm. of pressure when the patient was in the recumbent position. There was conduction deafness associated with vestibular hyperexcitability. Operation showed a dilated right ventricle, and injection of air was followed by an immediate reaction consisting of headache and vomiting. A trephination of the left parieto-occipital region showed that the dura was tense and the convolutions were enlarged. The visual disturbances persisted, but before another operation could be performed erysipelas developed and the patient died. Autopsy revealed extensive inflammatory lesions in the meninges about the base, together with granular ependymitis blocking the aqueduct of Sylvius. The choroid plexus showed peculiar infiltration; it was thickened, adherent and firm, and filled the lateral ventricles. It appeared yellowish brown and could not be dissected from the neural parenchyma. Microscopically, there were marked fibrosis, infiltration and formation of many concretions and obliteration of the vascular pathways. The nature of the process was not clear, and no organisms were found in the sections. It was thought, however, that tuberculosis could be excluded.

A PECULIAR DEGENERATION OF THE GLOBUS PALLIDUS AND DENTATE NUCLEUS MANIFESTED CLINICALLY BY PHENOMENA OF MOTOR EXCITATION AND NEUROMUSCULAR HYPEREXCITABILITY AND BY TERMINAL SYNDROME OF HYPERSENSITIVITY. G. GUILLAIN, I. BERTRAND and L. ROUQUÈS.

A boy aged 15 suffered from epileptiform attacks with muscular hyperexcitability resembling tetany for a year and a half. Later a syndrome of intracranial hypertension necessitated a decompression, but death soon followed. Autopsy showed neither tumor nor serous meningitis, but at the level of the globus pallidus and of both dentate nuclei were concentric calcareous bodies located almost exclusively in the adventitia of the vessels. A small lesion of a similar character, but representing a different stage of development, was found near the cortical surface in the frontal lobe. There was no inflammatory reaction, and the possibility that a mycotic infection was responsible for the change seemed to be excluded.

A CASE OF SYPHILITIC SPINAL AMYOTROPHY. J. A. CHAVANY and J. LEMANT.

A man aged 66 noticed weakness of the left arm in lifting a weight of 20 Kg. Several days later pains appeared in the left arm, but atrophy became apparent only seven months after the onset. Two months later pain and weakness began in the right arm. There was also evidence of some trophic disturbances. Examination showed weakness and atrophy of the biceps, deltoid and brachioradialis muscles and fibrillation on both sides. The tendon reflexes were increased in the arms but normal in the legs, except for a Babinski sign on the left. Sensibility was normal, as were the pupils. The Wassermann reaction of the blood was positive, but that of the cerebrospinal fluid was negative. Injection of iodized

poppy-seed oil 40 per cent into the cisterna showed a partial arrest of the opaque medium in the lower portion of the cervical region. The underlying disorder was considered to be syphilitic meningomyelitis.

MENINGIOMA IN CHILDREN. T. DE MARTEL and J. GUILLAUME.

A girl aged 10 years complained of frontal headache in the morning and occasional vomiting. Ophthalmologic examination revealed bilateral choked disks; vision in the right eye was reduced to perception of light. No signs of focal involvement were present, but roentgenograms showed indications of intracranial hypertension. A ventriculogram showed a tumor in the right frontal region. The ventricles were drained for forty-eight hours before exploration. The tumor when removed weighed 280 Gm. Recovery occurred without complications. Histologically the tumor was a characteristic meningoblastoma. The authors state that meningeal tumor in children is rare, but they presented a similar case in April 1934.

TUBERCULOMA OF THE PARIETAL REGION REMOVED SURGICALLY. P. SCHMITE.

A woman aged 26 complained of convulsive seizures and weakness of the left side of five months' duration, the disturbances having appeared shortly after delivery of a healthy child. A preliminary decompression was performed on account of the poor condition of the patient, and about a week later the tumor was exposed at a depth of 1 cm. beneath the cortex and removed by electrocoagulation and suction. The patient had no seizures after the operation, but the paralysis persisted. Tuberculous meningitis did not develop. Though a definite prognosis could not be made at the time of the report, hopes for a satisfactory outcome appeared justified. The tumor proved to be a characteristic tuberculoma.

CONGENITAL MENTAL DEFICIENCY WITH HYPERTONIA AND PARATONIA, OPPOSITION AND NEGATIVISM: STUDY OF THE BLOCK REACTION. P. R. BIZE.

According to Dupré, paratonia is a variety of muscular hypertonia in relation to intentional movement and preventing voluntary muscular relaxation. To elicit the sign peculiar to the disorder the patient is asked voluntarily to relax the arm, "to let it go dead." In the paratonic person this maneuver elicits a muscular contraction, the intensity of which is proportional to the efforts of the subject to secure relaxation. There is thus an insufficiency in the power of voluntary inhibition, and the condition can be regarded as a "subpsychic" disorder. The patient studied, a mentally defective child aged 15, showed hypo-extensibility of the flexor muscles and limitation of dorsal movements of the wrist and of separation of the fingers. Muscular relaxation could not be obtained spontaneously. All efforts to elicit it met with increased muscle tone. There were, however, a Babinski sign on the right and synkinetic movements. The patient presented many mannerisms and marked negativism in addition to the mental debility.

SYRINGOMYELIA WITH CHEIROMEGALY: THE RÔLE OF INJURY IN SYRINGOMYELIA. LHERMITTE and A. NEMOURS.

A man aged 53 noticed that his hands were becoming thick, massive and deformed. Edema was also present in the legs, and there was a curvature of the upper part of the thoracic portion of the spine. Fibrillations were observed in the deltoid and biceps muscles. For seven years the patient had suffered from hiccups associated with a sensation like an electric discharge running from the neck to the feet. Sensory examination showed characteristic syringomyelic dissociation. The reflexes were absent in the arms and exaggerated in the legs. The history stated that on five different occasions the patient had sustained moderately severe injuries about the shoulders, back and hands. From the time of the first accident,

sustained at the age of 16, it was noted that sensibility to pain was decreased in the hands. Roentgen irradiation produced some improvement in motor power but not in other functions.

ANTAGONIST REFLEXES IN PARKINSONISM. J. TINEL, M. FORESTIER and E. FRIEDMAN.

Tinel, Forestier and Friedman call attention to a reaction found especially in parkinsonism—contraction at the level of the antagonistic muscles accompanying the reflex response of the agonistic muscles tested. For instance, when the knee jerk is obtained, the reaction is present in the hamstring muscles; this may be a satisfactory test for rigidity due to extrapyramidal involvement. It may underlie the phenomenon of the cogwheel rhythm that is present also in cases of such involvement. The phenomenon has been described under a number of different headings but has not received detailed study. In a normal subject the contraction of the hamstring muscles is measured at the same time that the patellar reflex is obtained; there is rather slight contraction even though the lower portion of the leg is prevented from moving. In parkinsonism there is marked exaggeration of the reaction, and on repeated tapping the reflex of the antagonist becomes even more marked, whereas in the normal person it tends to die out. This reflex is not found in ordinary spastic hemiplegia. Sometimes the summation of the reflex may cause more or less constant hypertonia of the hamstring muscles. This summation is not observed on faradic stimulation at the same rate as the percussion of the patellar tendon. Similar reflexes are to be found at the elbow and at the ankle and wrist. The authors express the belief that the response under consideration is one of the most characteristic and most easily elicited reactions in cases of extrapyramidal disorders.

CONTINUOUS RHYTHMIC MYOCLONIA PRODUCED BY SURGICAL INTERVENTION ON THE BRAIN STEM. P. DELMAS-MARSALET and L. VAN BOGAERT.

A woman aged 31 suffered from parkinsonism which developed after she had encephalitis eight years previously. The patient was bedridden, helpless, speechless and rigid; she showed tremor of the lips and of all four limbs, which was exaggerated on movement. An attempt was made to expose the dentate nucleus. During the operation the patient experienced formication in the right limbs and at the same time moved them voluntarily with much greater ease. The left limbs also appeared less rigid, and the elementary postural reflexes were immediately markedly diminished on both sides. On the following day it was obvious that there was marked reduction in the rigidity on both sides, but in the left leg there were violent myoclonic contractions at the rate of 160 contractions per minute; in addition, there was rotatory, clockwise nystagmus, the rate being 200 rotations per minute, and the patient had difficulty in swallowing. She was unable to eat or sleep and died about ten days after the operation. At necropsy partial softening was noted in the territory of the superior cerebellar artery, associated with destruction of the white matter underlying the superior lateral lobule and the dentate nucleus. There was also involvement in the distribution of the short circumferential artery of the middle cerebellar peduncle. The important feature of this unfortunate surgical intervention seems to be its relation to the myoclonia. The lesions in the olive were considered to have developed later than the myoclonic syndrome, since the movements were present the day after operation. Nevertheless, the contralateral olivary body was already undergoing certain degenerative changes. The nystagmus was apparently due to a massive lesion of Deiters' and Bechterew's nuclei. The central tegmental fasciculus in this case was not involved.

SO-CALLED MENTAL ANOREXIA AND THE HYPOPHYSIS. COSSA and BOUGEANT.

The important rôle of the anterior lobe of the hypophysis has caused an examination of so-called functional anorexia. A girl aged 17 with a background of

family maladjustment suffered characteristic hysterical anorexia associated with vomiting. The menstrual flow was suppressed, and the weight fell to 44 Kg. As a result of a short rest cure and injections of insulin, anterior pituitary substance and estrogenic substance the patient's weight rose to 57 Kg.; her appetite increased markedly and the neurotic signs disappeared. Testing of the influence of the various drugs seemed to point to the hypophyseal extract as being the important drug in producing this satisfactory result.

PECULIAR NERVOUS CRISES AND TOTAL CALORIC VESTIBULAR AREFLEXIA AS EARLY SIGNS OF A SURGICALLY VERIFIED TUMOR OF THE FOURTH VENTRICLE. J. A. BARRÉ, JEAN MASSON and A. CHARBONNEL.

In December 1934 a boy aged 6 years began to suffer from peculiar nervous crises characterized by severe rotary vertigo, epigastric pains, pallor, loss of consciousness and, occasionally, vomiting. There was a tendency for the head to be cocked toward the right side, and there was complete and bilateral areflexia to temperature. Later the gait became definitely of a staggering type. The patient was operated on, and a tumor was found adherent to the floor of the fourth ventricle and invading the right lobe of the cerebellum.

KORSAKOFF'S PSYCHOSIS COMPLICATING SUPPURATIVE TUBERCULOUS LYMPHADENITIS. L. BÉTHOUX.

A woman aged 49, of tuberculous stock, who had been scrofulous since childhood, presented polyneuritis and psychic manifestations associated with a suppurative submaxillary adenitis in which tubercle bacilli were found. The patient was not alcoholic. Under treatment the patient gained 10 Kg.; the suppuration ceased; the psychosis disappeared, though amnesia for the early part of the psychosis persisted, and the signs of neuritis gradually disappeared, when the patient left the hospital there was still a disturbance in the reflexes of the legs.

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CEREBRAL HEMORRHAGES IN YOUNG PERSONS OPERATED ON FOR OLD VENTRICULAR DILATATION DUE TO STENOSIS OF THE FOURTH VENTRICLE: RÔLE OF POSTOPERATIVE VENTRICULAR DEPLETION IN THE PATHOGENESIS OF THESE ACCIDENTS. M. DAVID, H. BERDET, D. MAHOUDEAU and H. ASKENASY.

In autopsies on patients dying a few days after operation for a block in the fourth ventricle, hemorrhagic areas are sometimes noted scattered through the cerebral hemispheres. This appears to be due not to arterial hypertension but to some disturbance in the intracranial pressure, particularly as in all cases the ventricles have been dilated for a prolonged period. It seems probable that the collapse of the ventricles following operation is of an importance analogous to that which obtains in the bladder or thorax when tension is relieved suddenly and completely. The authors report three cases in detail in which death occurred shortly after operative intervention in the posterior fossa. However, it is fairly common to find in performing an encephalography by the lumbar route that after removal of a fairly large quantity of fluid the fluid becomes blood-tinged even though no more air is added. It seems possible that there is an indirect action on centers of the diencephalon which have already been injured by the long continued hydrocephalus. Two of the patients had black vomit, which is a grave prognostic phenomenon likely to be present when the hypothalamus is injured. The hemorrhage in these cases appears to be of venous rather than of arterial origin and seems also to occur electively in the area drained by the vein of Galen. The authors state that to avoid such accidents it seems better to drain the ventricles for a while before operating or to inject fluid into the collapsed ventricles at the end of operation and during ensuing days.

PARKINSONISM DUE TO NEURORECURRENCE. W. PIRES.

A Brazilian mulatto aged 32 had contracted syphilis five years previously and later suffered from headache and rheumatic pains. He received fifteen injections of a preparation of mercury and six of neoarsphenamine, which gave him complete relief from the pains. Three months after the last injection he noticed some rigidity in the right arm, and stumbling began and continued to develop into the characteristic symptoms of parkinsonism. Examination showed a sluggish reaction of the pupils to light. The blood and spinal fluid showed characteristic signs of neurosyphilis; the spinal fluid contained 113 cells per cubic millimeter, and the colloidal gold curve was of the end-zone type. Pires states that similar cases have been reported before and that in one of them the symptoms disappeared after malarial treatment.

A NEW SYNDROME OF CEREBELLAR ATAXIA. D. PAULIAN and M. CARDAS.

A girl aged 14 at the age of 3 years had suffered from an acute exanthem and at 5 years experienced mild titubation and intention tremor. She was clumsy in walking and running; later nasal speech developed, but there were no abnormal movements. The right pupil was larger than the left, but the reactions were normal; there was no nystagmus. On the left side the lower part of the face was slightly weak; the tongue was normal, and the uvula moved in the midline; there was abolition of the pharyngeal reflex. The patient suffered an occasional reflux of fluid from the nose. There were loss of the tendon reflexes, hypotonia, a Romberg sign and active abdominal reflexes. In both upper and lower limbs there was marked ataxia without any disturbance in sensibility. The family history and serologic examination yielded no data of importance. Paulian and Cardas state that it is a problem to decide whether the symptoms represented a combination of Friedreich's ataxia and cerebellar heredodegeneration, developing without known family history, or whether they represented the effect of a virus attack on the nervous system. If the latter hypothesis is correct the virus at first gave marked dermatotropic symptoms and later affected the nervous system.

TUMORS OF THE AMYGDALA. T. DE MARTEL and J. GUILLAUME.

When a tumor involves one cerebellar hemisphere it is not exceptional to observe infiltration of the superior part of the amygdala, but in the two cases reported the tumor developed exclusively in one tonsil, which became engaged in the foramen magnum and extended down the cervical canal to the third vertebral segment. The first case was that of a man, aged 34, who complained of attacks of pain in the left cervical region radiating toward the top of the head and along the lower border of the jaw. They came on almost exclusively when the patient was lying down or when he flexed his head forward. During attacks the patient carried his head somewhat flexed anteriorly and tilted toward the left shoulder. Six months after the onset there were transient diplopia and reduction in vision, especially on the right, and shortly before the patient came under observation there developed staggering, difficulty in swallowing and occasional vomiting. Examination revealed bilateral choked disk, normal ocular movements and mild hypotonia of the left side of the palate and tongue. There was slight nystagmus on looking toward the right, and the patient showed a tendency to fall toward the right and backward. During ventricular puncture the patient noted relief from the headache and pain in the neck, and a ventriculogram confirmed the diagnosis of tumor of the posterior fossa. At operation the tumor was found in the left amygdala, extending down through the foramen magnum. It was extirpated apparently completely, and the patient recovered.

In the second case the disorder was similar, and the patient likewise made a satisfactory recovery. In both cases the primary symptoms appeared to be due to irritation of the posterior roots of the upper cervical region, and later disturbances, to interference with the circulation of the cerebrospinal fluid.

DETROIT SOCIETY OF NEUROLOGY AND PSYCHIATRY

Regular Meeting, Nov. 7, 1935

LEO H. BARTEMEIER, M.D., *Presiding*

A PSYCHOANALYTIC STUDY OF A PATIENT WITH EPILEPSY. DR. LEO H. BARTEMEIER.

A single girl aged 20 was referred for therapeutic analysis. Within twenty-four hours after she had been rejected by a lover for a girl whom she regarded as inferior to herself, she began to have nocturnal convulsions of the grand mal type. After about ten days she began to experience attacks of a petit mal type in the daytime. Under treatment with phenobarbital, the grand mal seizures disappeared, but the medication had no effect on the petit mal attacks. There was no family history of epilepsy and no history of trauma to the head. The patient had had no convulsive disorder in childhood. In the analysis it became clear that the petit mal seizures were unconscious equivalents of masturbation. She was observed in several attacks during treatment. The petit mal seizures were provoked by her own fantasies or by remarks of others; they represented a flight from unconscious oral aggressive impulses toward her mother. These attacks were characterized by great variability in their manifestation. Certain features observed in the attacks were inclusions of previous behavior patterns. According to the present classification, the petit mal seizures are one of the manifestations of conversion hysteria.

During analysis the use of phenobarbital was discontinued. This resulted in an aggravation of the grand mal convulsions, and new symptoms, which included biting the tongue and drooling appeared. When the administration of phenobarbital was resumed, severe seizures disappeared. After the patient had been under analytic treatment for about two months it was possible to discontinue the treatment with phenobarbital without a recurrence of the nocturnal attacks.

The patient was of an oral type. She had always hated her father and had treated all men as women. She would tease them into being aggressive with her, and as soon as they became too masculine she slapped them and turned to a girl friend, with whom she could play the masculine rôle. This manifestly homosexual relationship disappeared in the course of treatment. She came to accept her femininity and developed a friendly relationship with her father.

It was thought that when she was rejected by the lover she took flight from the field of genitality altogether and regressed by means of the grand mal attacks to the time when she was receiving oral satisfaction. She always slept with her mother, and the grand mal attacks occurred only during sleep. After their occurrence had enabled her to attain a degree of convalescence she approached the genital problem once more, this time very cautiously because of her previous hurts and through the petit mal attacks in which she could often see without being seen. She thus attempted to regain her health as she had once attempted to gain maturity, i. e., by regressing to the earliest forms of gratification.

A year and a half has elapsed since the completion of the analysis; during this period the patient has been free from both petit mal and grand mal seizures, and the family regard her as cured of the symptom which brought her for treatment.

It is suggested that the information obtained in the treatment of this patient furnishes a clue with regard to petit mal and grand mal epilepsy. Grand mal attacks, which are characterized by sterotypy, represent regressions to the pregenital phases of ego-libido development; they are stereotyped because the life experiences are highly limited at that period of growth. The petit mal attacks are as variable as the person who suffers from them because their vocabulary is the vocabulary of his own life experiences. They represent reactions to frustrations

at a genital level and are to be thought of in terms of conversion hysteria. They are therefore not as amenable to medicinal therapy as are the grand mal attacks, in which the medication given orally has the neurotic significance of nursing.

THE SOCIOLOGY OF CONVULSIVE DISORDERS. DR. DAVID R. CLARK.

A convulsion is a symptom arising from irritation of the cells in the central nervous system. It is a conservative mechanism, the aim of which is the destruction of the irritant through hyperoxidation, regardless of the origin. Given a known irritant, the defining of the convulsion as a symptom becomes easy. Given unknown irritants (and they appear to be legion), the term epilepsy applies. Epilepsy appears to be a multiplicity of disorders with one common symptom, the convulsion. Cases were cited in which characteristic changes and conduct disorders were present, and, for contrast, cases were cited in which they did not appear, it being suggested that a widely differing, if unknown, etiology was present.

In some instances in which convulsions are associated with an element of social uncontrol and danger, the only practical solution is commitment of the person to an industrial disciplinary institution. Disciplinary institutions are populated largely by persons who are mentally defective. The population is exactly similar in principle, if not in type, to that of institutions for the confinement of persons with mental disease. This leads to the thought that one would do well to give up ideas of penal reform and adopt the view of medical quarantine of socially defective persons.

Book Reviews

Outlines of General Psychopathology. By William Malamud, M.D. Price, $5. Pp. 462. New York: W. W. Norton & Company, Inc., 1935.

Any attempt to reconcile the welter of conflicting points of view in the field of mental disorders and at the same time to maintain an attitude of objectivity conforming to the general precepts of science is welcome. This book is such an attempt. Its broad biologic approach and its adherence to scientific methodology and logic suggest that psychopathology has no need for radical departure from a systematic treatment of its data. Giving fair consideration to all contributions to the field, carefully distinguishing between objectively observable facts and theory and frankly admitting ignorance when no knowledge exists, the book is well worth while.

In analogy with general pathology, Malamud seeks to distinguish psychopathology from psychiatry on the basis of differences in aim. Psychopathology is defined as a "science that deals with the recognition, description, classification and understanding of phenomena of abnormal mental activity." This does not mean merely that it seeks purely psychologic explanations of abnormal mental activity, since then it would deal with a restricted part of psychology. Nor does it mean that psychopathology can replace psychiatry, in which the emphasis is on treatment. From this point of view psychopathology occupies a place between psychology and medicine. Its goal is to study phenomena as expressions of adjustment of a changed organism to a new set of circumstances. This includes single phenomena which occur in persons still considered as making an adjustment or responding with a total reaction medically, legally or sociologically within the range of the normal. With this objective, psychopathologic data would not be organized along accepted lines of classification of mental diseases or considered, as in psychology, merely as deviations from the normal.

In his definition of psychopathology Malamud follows Bernard Hart, who took Karl Pearson's definition of science as a starting point. After outlining the purposes of psychopathology as an independent science and attempting in this manner to define its field and goals, the author divides the work into three parts. The first deals with phenomenology. In the second part the determinants, pathogenesis and relationships of psychopathologic phenomena to the environment are discussed. After a review of some of the current theories of personality structure Malamud proposes a new one of his own. Finally, with this theory as a basis, the last part consists of an attempt at what Malamud calls synthesis of psychopathologic material, which amounts to an attempt to fit psychopathologic reaction types into a system required by his theory.

The phenomena of abnormal mental activity are divided into three groups: behavior, experiences and the physiologic concomitants of either one or both of these. Behavior is defined as "the observable reactions of an individual in a given situation." Experiences are those phenomena which admittedly are not capable of direct observation but which may be learned only through the report of the person as the subjective counterpart of his behavior. Their existence nevertheless can be ascertained in different persons in response to more or less similar situations. Such phenomena as changes in the pulse rate, respiration and blood pressure and electrical changes, which may accompany behavior or experience, are designated by the term physiologic concomitants.

In the section dealing with phenomenology, each of these groups is further subdivided. This is done largely for convenience of presentation, and it is constantly emphasized that such isolation of phenomena is arbitrary. Nevertheless, it is of value in furthering clarity of thinking and systematization in a field already

sufficiently confusing and confused. Thus, for the purposes of description behavior is considered as having general and special aspects. Disturbances in such fundamental characteristics as quantity, quality and the direction of activities are described as the general aspects of behavior. The special components of behavior include the observable disturbances in reception, intellection and expression. It is only the disturbances in these three essential components of behavior which are apparent to an outside observer that are dealt with here.

One example will suffice to illustrate the completeness of the author's outlines of the data. Under expression are discussed disturbances in motility, speech, organized forms of motor expression, instinctual expressions, complex acts and sleep. Each of these is further subdivided and considered. Disturbances in one of these—organized motor expressions, for example—include disturbances in gesture, coordination, gait, posture and station, writing, artistic expressions and emotional expression.

Disturbances in the subjective counterpart of behavior are presented in a similarly organized and systematic manner. The general aspects, such as disturbances in attitude of the person toward a situation, an environment and himself, are considered first. As special types of psychopathologic disturbances in the field of experience are grouped abnormal phenomena in subjective evaluation. Disturbances in the subjective components of reception are treated as changes in the sense of reality, in the feelings and in perception. The abnormal phenomena in the field of subjective evaluation are divided arbitrarily on the basis of what the author terms the preservation or loss of subject-object differentiation. By this criterion of the retention or loss of the ability to distinguish objectively valid conclusions from purely subjective experience, Malamud separates the phenomena of actual distortion of reality from milder disturbances usually termed psychoneurotic manifestations, such as phobias and obsessions, and includes a class of phenomena transitional between the two.

The section on physiologic concomitants does scarcely more than call attention to changes in respiration and in the cardiovascular, secretory and excretory functions, as well as to more recent observations in electrophysiology and pharmacodynamics. It refers the reader to works treating this material more adequately and emphasizes the caution necessary in the evaluation of the relationship of these concomitants to other phenomena of abnormal mental activity.

In the section dealing with determinants and pathogenesis Malamud attempts to find a method of systematization of material frankly admitted to be inadequate for complete understanding of the phenomena. After discussing various efforts to accomplish this, he proposes and adopts a division of the data into three categories: phylogenetic determinants, ontogenetic determinants and relationships within the situation. Briefly, these stand for constitutional, environmental and experiential factors in the development of psychopathologic phenomena. Pointing out that these categories are the same as those of determinants of normal adjustment and admitting that these categories are rather broad, he nevertheless argues that search for factors responsible for any phenomenon of abnormal mental activity must be limited within the range of these three possibilities. Among the most important contributions to the knowledge of phylogenetic or constitutional determinants Malamud places Jung's classification of mental types into extraverts and introverts and Kretschmer's grouping into physical types as perhaps the most useful. He considers that tendencies, probably hereditary, may under certain circumstances (and he emphasizes the need of these circumstances) be important though rarely predominant causative factors in the development of mental disease. In addition to general constitutional tendencies, the possibility that certain special types of psychopathologic phenomena, such as some sexual anomalies or tendencies to neurotic reactions, may be dependent on constitutional potentialities are also considered.

Among the ontogenetic determinants, physical or psychic, Malamud discusses three theories: the psychoanalytic theory, the theory of individual psychology and Pavlov's theory of conditioned reflexes. The chapter on relationships within the

situation discusses such factors as the social, the economic, the personal and the cosmic. There is included a discussion of the possible effects of changes of weather, climate and meteorologic conditions on the human organism. A chapter dealing with organic determinants in this section is of considerable interest because of the prefatory discussion of the perennially controversial antithesis of the organic and the psychogenic. Malamud concludes that one must consider phenomena as predominantly of one or the other category and "that it is doubtful whether an incontrovertible statement either one way or the other is essential in giving us an understanding of the organism as such." For the rest, organic determinants are considered as producing: (1) specific effects and (2) local manifestations.

Two current theories of personality structure, one of psychoanalysis and the other of Kahn, are presented briefly; both are found inadequate.

Malamud considers adjustment as expressive of the personality as a whole and not of any special sector in it, and regarding adjustment as a standard of comparison of different types of mental activity he states: "In its broadest sense adjustment can be regarded as the expression of the phenomenon characteristic to all individual entities, viz., the *urge to exist*." From this point of view the concept of adjustment is regarded as applicable not only to the activities of human beings but to all living organisms and to substance in general. Whether the methods utilized by any individual body in adjustment secure its existence or not does not change the fact that its beginning was in that direction. Naturally, the methods depend on the means at the command of the organism and on the situation to which adjustment must be made. Because these two factors cannot be easily separated, both the means available and the conditions of the environment are considered as one complex, called the adjustment organization. Malamud finds that for man two broad sets of methods may be determined: (1) those common to all individually existing bodies and (2) those peculiar to human beings as a specially organized group of living organisms. In following the evolutionary process by which the human being has finally acquired maturity, the author distinguishes three levels at which fundamental changes in organization have brought need for changes in methods of adjustment to be superimposed on and to modify those previously existing. He distinguishes three such radically different stages: "(1)The levels of *inorganic* matter; (2) the level of *organic* structure, which brings in the features of growth and multiplication, and (3) the level of *motile* organisms which brings with it the aspect of change from one type of environment to another." The controlling feature of the adjustment of the first level is self-assertion; that of the second, the tendency to grow and propagate, i. e., accretion, and that of the third, the appreciation of relationships as man moves from one set of conditions to another, this characteristic being broadly designated as ratiocination.

There follows a discussion of each of these methods of adjustment as exemplified by individual bodies showing predominantly each of these characteristics and the modifying influence of the superimposition in the hierarchy of the new method on the old: A solid inorganic body resists the tendencies of others to destroy it and thus evinces the characteristic of self-preservation or self-assertation in time; gas bodies manifest a second feature of self-assertion, that of self-extension, or self-assertion in space. In self-preservation the essential characteristic is passive resistance to environment; self-extension, on the other hand, is characteristically aggressive. Human beings manifest both passive resistance and aggressiveness, but because of a different form of organization these two "have been superseded by other forms of adjustment and express themselves under their control." Organic bodies, as contrasted with inorganic bodies, tend not only to maintain individuality, i. e., manifest the tendency of self-preservation, but also to occupy more space in growth and thus show in equal proportion with self-preservation a tendency to self-extension. As this is accomplished by aggression against surrounding bodies, it requires a new form of relationship with the outside, that of selection. Thus, in manifesting the feature of accretion, living bodies exercise choice. They divide

the environment into units which are acceptable and those which are rejected; it is in association with this need of selectively resisting and aggressively accepting other bodies that there arises the quality of interest in or a relation to different things in the environment. This is considered a prototype of affect in human beings and consists of a graded series of attitudes of acceptance and rejection toward other persons or things in the environment.

During growth the tendency for self-extension in space gains expression up to a limit set by the tendency for self-preservation. After this check the tendency to extension accumulates as unexpended energy which finally overcomes the self-preservative tendencies and, turning on the body itself, results in its splitting or multiplication. In this way the phenomenon of propagation appears. Since the splitting off of the new organism was primarily conditioned by an excess of aggressive tendencies, a trend to move apart from the group coexists with an attraction toward and a dependence on others, constituting a peculiar form of ambivalent attitude. This paradoxical combination of dependence and independence is most striking in those organisms in which motility is greatest, being least in evidence in such forms as plants. The fact that in most organisms propagation occurs as a result not of splitting but of the union of the sexes introduces still greater complexity into the problems of adjustment.

Ratiocination "consists of arranging the various contents of a situation according to their occurrence in time and space in logical categories of causality, meaning, value, and so on" and refers not only to external contents but also to occurrences within the individual person himself. "The urge for ratiocination arises in relation to all those activities that emanate from the functions of self-assertion and accretion and even out of ratiocination itself." In this sense it is the controlling feature of the mental activities of the human being.

The analogy to the concepts of psychoanalysis is obvious. Accretion and self-assertion are related to the unconscious, while ratiocination is at the conscious level of the personality, at which there is awareness of accretion and self-assertion, even if their processes are not represented in it. Tension arises when any one of the tendencies is opposed by either one or both of the others, while normal adjustment depends on a harmonious relationship between all three structures. A similar borrowed psychoanalytic theory is the dynamic concept that as a result of too great resistance from one level the energy pent up finds some form of expression in a weak spot in the repressing level. In normal persons such expression assumes the form of dreams and of errors, while in others there may be an open break against ratiocination, with resulting symptoms of mental disease.

One may ask whether the use of such anthropomorphic terms as self-assertion and adjustment in relation to nonliving bodies is justified. However, this concept is broad and obviously not dependent for substantiation on methods of investigation that are questionable as adequate tools of scientific study. The test of its validity naturally will come in the usefulness of its application to the phenomena in question by other students in future investigations.

In the section dealing with synthesis Malamud attempts to apply the theory. He considers the attempts of Bleuler and others to differentiate symptoms from the fundamental disturbance as essential for better understanding of the phenomena. To conceive of a fundamental disturbance in the personality as the basis for symptoms is not to confuse it with the etiology of the disturbance. Inflammation, for example, is a fundamental disturbance which is evidenced by certain symptoms, but the process of inflammation lies dynamically between the etiologic factor and the symptoms. With this in mind Malamud discusses psychopathologic reactions as being due fundamentally to disturbances in each of the three structures of personality, i. e., ratiocination, accretion and self-assertion, as well as a group of disturbances representing complex and transitional types.

An extensive glossary of psychiatric terms and a bibliography of one hundred and seventeen references serve to make the book valuable to the student reader.